

Original citation:

Kwon, J., Kim, S. W., Ungar, W. J., Tsiplova , K., Madan, Jason and Petrou, Stavros. (2017) A systematic review and meta-analysis of childhood health utilities. Medical Decision Making.

Permanent WRAP URL:

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Publisher's statement:

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Published version: <https://doi.org/10.1177/0272989X17732990>

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A Systematic Review and Meta-Analysis of Childhood Health

Utilities

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Word count: 6,218

ABSTRACT

Background: A common feature of most reviews or catalogues of health utilities has been their focus on adult health states or derivation of values from adult populations. More generally, utility measurement in or on behalf of children has been constrained by a number of methodological concerns. The objective of this study was to conduct the first comprehensive systematic review and meta-analysis of primary utility data for childhood conditions and descriptors and to determine the effects of methodological factors on childhood utilities.

Methods: The review followed PRISMA guidelines. PubMed, Embase, Web of Science, PsycINFO, EconLit, CINAHL and Cochrane Library were searched for primary studies reporting health utilities for childhood conditions or descriptors using direct or indirect valuation methods. The Pediatric Economic Database Evaluation (PEDE) was also searched for cost-utility analyses with primary utility values. Mean or median utilities for each of the main samples were catalogued, whilst weighted averages of utilities for each health condition were estimated, by valuation method. Mixed-effects meta-regression using hierarchical linear modelling was conducted for the most common valuation methods to estimate the utility decrement for each health condition category relative to general childhood population health, as well as the independent effects of methodological factors.

Results: The literature searches resulted in 272 eligible studies. These yielded 3,414 utilities when all sub-groups were considered, covering all ICD-10 chapters relevant to childhood health, 19 valuation methods, 12 respondent types, 8 modes of administration, and data from 36 countries. A total of 1,191 utility values were obtained when only main study samples were considered and these were catalogued by health condition or descriptor, and methodological characteristics. 1,073 mean utilities for main samples were used for fixed-effects meta-analysis by health condition and valuation method. Mixed-effects meta-regressions estimated that 53 of 76 ICD-10 delineated health conditions valued using the HUI3 were associated with statistically significant utility decrements relative to general population health, whilst 38 of 57 valued using a Visual Analogue Scale (VAS) were associated with statistically significant VAS decrements. For both methods, parental proxy-assessment was associated with overestimation of values, whilst adolescents reported lower values than children under 12 years. VAS responses were more heavily influenced by mode of administration than the HUI3.

Conclusion: Utilities and their associated distributions, as well as the independent contributions of methodological factors, revealed by this systematic review and meta-analysis can inform future economic evaluations within the childhood context.

Keywords: Systematic review; Meta-analysis; Meta-regression; PRISMA; Hierarchical linear model; Childhood health states; Health utility; Pediatric Economic Database Evaluation; Economic evaluation.

INTRODUCTION

Economic evaluation involves the comparative analysis of alternative programmes or interventions in terms of their costs and consequences.¹ It has increasingly been used to inform health care decision-making in the United Kingdom by bodies such as the National Institute for Health and Clinical Excellence (NICE) in England and Wales and the Scottish Medicines Consortium (SMC) for Scotland.^{2,3} Similarly, economic evaluation has increasingly been used to inform the health care decision-making processes of government agencies in other nations.^{4,5} The preferred measure of health outcome for many government agencies tasked with setting health priorities under conditions of finite resources remains the quality-adjusted life year (QALY), a preference-based measure of health outcome that combines length of life and health-related quality of life (HRQoL) in a single metric.⁶ For government agencies, the QALY has the advantage of allowing cost-effectiveness comparisons to be made across different health care interventions for disparate health conditions. For economists, it offers an additional advantage in that the techniques used to derive the QALY reflect, to varying degrees, people's preferences for health outcomes, thereby moving beyond the narrow biomedical model towards an extra-welfarist approach that informs allocative decision-making.¹

Health economists have developed a number of approaches for estimating preference-based HRQoL weights (or health utilities) associated with different health conditions (or health states) for inclusion within the QALY metric.⁷ These include scaling techniques, such as the Standard Gamble (SG) and Time Trade-Off (TTO) approaches;⁸ health rating scales, such as the Visual Analogue Scale (VAS); multi-attribute health status classification systems with preference scores, such as the EQ-5D,⁹ Health Utilities Index (HUI),¹⁰ SF-6D,¹¹ Quality of Well-Being Scale¹² and Assessment of Quality of Life (AQoL or AQoL-5D);¹³ and mapping from non-preference-based measures onto generic preference-based measures of health.¹⁴ As measurement of preferences and valuation occur in a single step, the SG, TTO and VAS methods are commonly referred to as *direct* valuation methods. In contrast, multi-attribute health indices with preference scores make use of classification systems for measurement and apply a pre-existing valuation or tariff set. These are commonly referred to as *indirect* valuation methods. Both direct and indirect valuation methods have been widely applied within health economic evaluations.⁷ However, there are several circumstances, particularly in the context of decision-analytic modelling based economic evaluations, where analysts lack the time and resources to obtain original health utility data for all health conditions or states of interest. In such cases, methodological guidance documents generally recommend that analysts: (i) resort to published literature for health utilities; (ii) use approaches for identifying and synthesising

health utilities evidence in accordance with the general principles of evidence-based medicine; and (iii) use methods that are justifiable and reproducible.¹⁵

A number of structured or systematic reviews of health utility values have been reported in the literature, the results of which have acted as data inputs into economic evaluations. Tengs and Wallace¹⁶ identified 1,000 original health utility values in 154 studies. Bell and colleagues¹⁷ conducted a systematic review of cost-utility analyses published between 1976 and 1997 and identified 949 health utility values in 228 studies. More recently, systematic reviews of health utilities have been reported for a number of specific clinical conditions, including but not limited to liver disease,¹⁸ neuropathic pain,¹⁹ Alzheimer's disease,²⁰ unipolar depression,²¹ colorectal cancer,²² HIV/AIDS,²³ breast cancer,²⁴ type II diabetes,²⁵ surgical site infection,²⁶ and Crohn's disease and ulcerative colitis.²⁷

A common feature of the vast majority of structured or systematic reviews of health utility values has been a focus on adult health conditions or states or derivation of values from adult populations. Reviews of health utility values for childhood health conditions or states have been limited to a small number of health conditions such as acute lymphoblastic leukaemia, asthma, cancer, diabetes and skin diseases.^{28,29} The recent review of health utilities in children and adolescents conducted by Thorrington and Eames³⁰ was restricted to evidence from 90 studies, and reports results by valuation method, country of origin and year of publication, rather than by health condition or state. Moreover, published catalogues of health utility values for childhood health conditions have been limited to a relatively small number of conditions valued using a single valuation method and a single source of values.³¹⁻³³ Another source of childhood utility values is the Paediatric Economic Database Evaluation (PEDE) project, a searchable online repository of paediatric economic evaluations including 784 cost-utility analyses published between 1980 and 2015 from which 1,842 utility weights are available.³⁴ However, only 72 of these cost-utility analyses estimated primary utility values from childhood populations or their proxies; the remainder derived utility weights from the literature, adult studies, or expert opinion.³⁵ This finding is consistent with an earlier review in 2012 by Kromm and colleagues³⁶ of 213 cost-utility analyses in PEDE published between 1997 and 2009: they found that only 16 analyses measured utilities from children or their proxies, 134 relied on author assumption or adult and/or paediatric literature and 13 used expert opinion. Even when utility weights are derived from the literature, a concern is that published cost-utility analyses often provide very little description of relevant design features surrounding the derivation of utility values. Moreover, the utility weights contained in PEDE are restricted to those extracted

from published cost-utility analyses, thus representing only one source of childhood utilities measured by primary studies.

Faced therefore with a paucity of reliable primary utility data for childhood health states and associated descriptors, analysts conducting cost-effectiveness modelling studies in child health have commonly applied health utility values derived for adults to childhood health states.³⁷ The concern is that analysts are overlooking a range of methodological concerns that are likely to reduce the suitability of adult-centred or adult-derived values for childhood health states. These include the relevant attributes to incorporate into measurement instruments, appropriate respondents for measurement exercises, potential sources of bias in the description and valuation processes, and the psychometric properties of existing measures.³⁸ These limitations have been mitigated to a degree by the development of childhood- and adolescent-specific multi-attribute health classification systems generating preference-based scores, such as the EQ-5D-Y (Youth),³⁹ 16-Dimensional Health-Related Measure (16D),⁴⁰ 17-Dimensional Health-Related Measure (17D),⁴¹ AQoL-6D⁴² and Child Health Utility 9-Dimensions (CHU9D),⁴³ recently reviewed by Chen and Ratcliffe.⁴⁴ Nevertheless, variation between measures in choice of attributes and their conceptual underpinnings, valuation protocol, choice of informant, appropriateness for each developmental stage, and formatting, is likely to independently impact on health utility values. To generate reliable results from paediatric cost-utility analyses that can inform health care decision making, it is important that analyses apply valid health utility estimates after accounting for influences of these methodological factors.

In this paper, we report the results of the first comprehensive systematic review of health utility values for childhood conditions and broader descriptors. The paper also reports meta-regressions that determine the effects of a range of methodological factors on these health utility values. It is anticipated that the results of this systematic review and meta-regressions will act as a significant new resource for analysts conducting paediatric cost-utility analyses.

METHODS

Systematic Review

The systematic review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.⁴⁵ A comprehensive literature search strategy was developed and piloted. The final search strategy applied an intersection of health utility, valuation method and childhood search terms, and is presented in full in the supplementary material. A separate search strategy that additionally applied ‘quality of life’ or ‘health-related quality of life’ search terms during piloting did not yield any additional relevant articles or reports (hereafter articles

for brevity), and was therefore not pursued. The following databases were searched: PubMed, Embase of OVID Medline, Web of Science, PsycINFO, Cochrane Library, CINAHL and EconLit. Searches of titles and abstract were applied to articles published online before 31st December 2015. Non-English language articles were excluded. A search of the PEDE database was also conducted to identify cost-utility analyses published between 1980 and 2015 reporting health utilities for childhood conditions or broader descriptors.

The main inclusion criteria for the search strategy were primary studies reporting health utilities for childhood populations or for childhood conditions or descriptors using direct or indirect valuation methods. Duplicates of identified articles were removed using EndNote version 7.7. Previous related literature reviews^{28-30,46-48} were excluded, but used for manual reference searching. Titles and abstracts were assessed at the first stage of the review by two independent reviewers (JK and SWK). If an article received two approvals, it proceeded to the next stage, with disagreements referred to a third reviewer (SP) for the final assessment. The same reviewers searched full-text articles at the second stage of the review with disagreements again referred to the third reviewer for final assessments. We excluded studies at the full article stage that were: (1) not published in the English language; (2) decision-analytic modelling based economic evaluations that relied purely on secondary data; (3) studies that reported only single-attribute scores for indirect utility instruments; or (4) studies where the main samples had a mean or median target age exceeding 18 years. Conference abstracts were included if they reported original health utility values. Similarly, studies reporting primary VAS scores were included despite disagreement amongst many health economists about their theoretical basis for QALY construction.⁴⁹

Data Extraction

From each article that met the study selection criteria, we extracted the following information about the characteristics of the study using a bespoke proforma: (1) bibliographic details, including year of publication; (2) country/geographical jurisdiction; (3) setting (hospital inpatient ward, hospital outpatient clinic, general practice, school, via post, via internet, other); (4) health descriptor(s), which could take the form of a health condition/disease, health state or intervention descriptor; (5) respondent type (self-assessment by children, proxy-assessment by parents, caregivers, nurses, physicians, other proxies); (6) age of target childhood group (reported as age at diagnosis, age at study, and associated descriptive statistics); (7) size of study population; (8) direct valuation method applied (if applicable); (9) indirect valuation method applied (if applicable); (10) utility tariff if indirect valuation method applied; (11) utility or VAS scores (including central statistics and measures of variability); (12) study design

(cross-sectional study, clinical trial, prospective observational, internet survey, other); (13) response quality (response rate, information on dropouts, reasons for loss to follow-up, etc.); (14) statistical method for analysing utilities; and (15) any reported methodological concerns. A point was given to the reporting of each of these characteristics, and the total points were interpreted as the overall reporting quality score. All data were entered into an Excel database.

After completing the database, a subset including only data for the main study samples within each article was created. This subset excluded data for any potentially overlapping sub-samples based on sociodemographic characteristics, for example, gender or age. If an article reported utility or VAS scores for a health condition or descriptor using two or more valuation methods or two or more respondent types, each set of utility values was treated as a separate main sample. For randomised controlled trials or prospective observational intervention studies, only pre-treatment values were treated as main samples. This was to reduce a further layer of confounding introduced by intervention effects. Finally, only samples reporting mean or median utility or VAS scores associated with an identifiable health condition or descriptor were included as main samples. This meant exclusion of samples reporting only mean change in utility or VAS score or regression coefficients.

An International Classification of Diseases 10th revision (ICD-10) code was allocated to each sample within the database. Where data permitted, health conditions were characterised by (i) ICD-10 chapter; (ii) ICD-10 sub-chapter encompassing a range of ICD-10 codes; and (iii) specific ICD-10 codes. Any health condition with three or more main study samples reporting mean utility or VAS scores (i.e. excluding median utility or VAS scores) was treated as a unique health condition category within an ICD-10 chapter. If a health condition contained two or less main study samples, it was grouped with other health conditions at the more aggregate level of the ICD-10 sub-chapter. The categorisation of childhood health states was subsumed into the above process.

Statistical Analysis

Two broad statistical analysis approaches were followed. For both approaches, only the main samples reporting mean utility or VAS scores were used (for completeness descriptive statistics for sub-samples are reported in the online Excel database at <http://childhoodutilities.wordpress.com>). The first approach estimated weighted averages of mean utility or VAS scores for each health condition category, by valuation method (a fixed-effects meta-analysis). Each mean utility or VAS score was weighted by the inverse of its sample variance, defined as the square of the standard error of the sample mean.⁵⁰

The second analytical approach used a hierarchical linear model (HLM) in a linear mixed-effects meta-regression.²²⁻²⁴ The aim was to estimate the utility or VAS score decrement of each health condition category relative to general population health, after controlling for methodological factors and study-specific random effects not accounted for by the explanatory variables. HLM introduces three levels of random variation. First, the variation of the observed mean utility or VAS score around the true mean value; second, the within-study variation in true mean value after controlling for explanatory variables; and, third, the between-study variation in true mean utility or VAS score after controlling for explanatory variables. Hence, the model allows for both within-study clustering and between-study variation in utility or VAS score.²³ Analyses were restricted to main samples using the two most common valuation methods within the dataset, namely the Health Utilities Index Mark 3 (HUI3) and VAS variants (including standard VAS, EQ-5D VAS and EQ-5D-Y VAS). The rationale is that we expected valuation method to exert an independent effect on utility or VAS score, and that this effect might vary across health conditions.⁵¹ Hence, each analysis was restricted to samples covering all health conditions, but using a single valuation method. Mean utility or VAS scores were weighted by the inverse of their standard error, whilst individual studies were weighted by the total number of their respondents. Health condition categories, respondent types and modes of administration entered both HUI3 and VAS models as indicator variables. Both models also included a dummy variable for samples valuing hypothetical health states, a dummy variable for samples with minimum age greater than 12 years, and a dummy variable for samples from developing countries. All statistical analyses were conducted using STATA software, version 14 (Stata-Corp, College Station, Texas, USA).

RESULTS

Systematic Review

Figure 1 illustrates the flow of the systematic review process. The literature search resulted in 27,119 individual articles. The first stage review of titles and abstracts excluded 26,634 articles. The main reasons for exclusion were targeting of non-childhood populations and use of non-preference-based health outcome measures. Before the second stage review of full articles, 40 articles (mostly conference abstracts) could not be accessed online. Of the 485 articles that progressed to the second stage, 214 were included in the final sample for data extraction. This sample included 14 conference abstracts. Manual reference searching based on these 214 articles and previous systematic reviews^{28-30,46-48} yielded 43 further articles, whilst a search of the PEDE database yielded a further 15 articles. Thus, data was extracted from 272 primary

studies of health utilities for childhood conditions or descriptors. Appendix A summarises each of the 272 studies included in the systematic review by health condition, healthcare intervention where relevant, country of origin, country of tariff population, valuation method, respondent type, mode of administration, and age of target population. Appendix B provides the full references for each of these studies. The Excel database at <http://childhoodutilities.wordpress.com> summarises the characteristics of these studies with explanatory notes for navigation.

Health Conditions by ICD-10 Chapter

Table 1 summarises the results of the systematic review by ICD-10 chapters and health condition categories. Numbers of samples in each category are provided in the final column, whilst numbers of main samples reporting mean utility or VAS scores are provided in the parentheses in the same column. Health conditions with two or less main samples were grouped with other conditions within the same ICD-10 sub-chapter. For example, sickle cell disease (ICD-10 code 3-D57), favism (3-D55) and thalassemia (3-D56) were grouped in category 3.2 representing ICD-10 sub-chapter for haemolytic anaemias (3-D55-D59) since each contained two or less main samples reporting mean values, and they were all characterised by the same ICD-10 sub-chapter. When conditions with two or less main samples were grouped together despite having ICD-10 codes that crossed ICD-10 sub-chapters, the resulting category was classified as “other type”, as in categories 2.12, 4.8, 5.8, 7.2, 11.4, 14.4, 17.3 and 19.3. Exceptions to these grouping rules were categories 1.8, 1.9, 2.6, 3.3, 11.2, 11.3, 12.2, 12.3, 16.4, 21.2 and 21.3, where these conditions were deemed to be too dissimilar to be grouped together with another condition within the ICD-10 chapter. They are hence presented as unique categories despite having two or less main samples. Where health condition categories have been classified as “combined” (e.g. categories 2.1, 2.2, 19.1, 22), each sample contains patients of diverse health states. The Excel database should be referred to for information on each sample.

The largest number of samples are contained in category 0 representing general population health. This category contains samples of children and/or adolescents drawn from the general community or schools or control groups of healthy children within observational studies. Category 21 classifies samples by healthcare intervention rather than disease type. These samples are drawn from studies delineated by interventions or programmes and health condition is not specified.

Across all 101 health condition categories, there were 3,414 samples in total, 1,191 if only main samples reporting mean or median utility or VAS scores were considered, and 1,073 if

only main sample reporting mean values were considered. Inclusion of only mean values in the meta-regressions meant that some health condition categories were excluded, e.g., categories 1.9 for chickenpox and 11.5 for celiac disease.

Disentangling potential intervention effects when selecting main samples was an imperfect process. For example, low birthweight or preterm children had often received paediatric intensive care, and hence main sample utility or VAS scores in categories 16.1, 16.2 and 16.3 may have captured past intervention effects. Similarly, main sample utility or VAS scores in categories 9.3 and 14.1 may have captured the effects of organ transplants many years before the conduct of the observational studies.

Study Characteristics

Table 2 summarises the samples included in the analyses by valuation method, respondent type, mode of administration, minimum age of children in sample, and country of origin. The most commonly used direct valuation method was VAS (including standard VAS, EQ-5D VAS and EQ-5D-Y VAS), which was applied in 601 samples (247 main samples reporting mean or median utility or VAS scores). The most commonly used indirect valuation method was the HUI3.

Samples using the 15D, 16D or 17D were grouped together, even though each instrument is targeted at different age groups. One study used a 10-dimension variant of the HUI,⁵² whilst another assumed the value 0 indicated the worst imaginable health state rather than death for the HUI3.⁵³ Samples from both studies were classified under a “Modified HUI” valuation method. The review included only one preference-based condition-specific instrument, the Pediatric Asthma Health Outcome Measure (PAHOM), developed by Chiou and colleagues.⁵⁴ Three studies mapped clinical measures for depression onto utility indices.⁵⁵⁻⁵⁷ Their samples were classified under the “Utility from non-preference-based measure (NPB)” category.

The respondent type with the largest number of main samples was proxy assessment by parents (n=408), followed by self-assessment by children and/or adolescents (n=349). In 151 main samples, parents or caregivers valued the health states together with children. Types of proxy respondents varied widely, and included parents, caregivers, healthcare practitioners, the general public, and adult patients with the same disease.

Modes of administration were grouped under self-administration and interview-administration. The most common mode of self-administration was non-postal survey (paper questionnaire) completed in a clinic or school. One study by Lee and colleagues⁵⁸ used a Delphi survey of clinicians. Face-to-face interview was more widely used than any other mode of interview administration.

Over one half of all samples (n=1,856) valued health states for children under 12 years. 1,307 (70%) of these samples used a form of proxy-assessment. Similarly, 146 of 220 (66%) samples that contained infants (minimum age of 0) valued hypothetical health states using proxy-assessment. A significant number of samples (n=508) did not specify the target age.

The largest number of samples was surveyed in Canada, followed by the US and the UK. There were 3,153 samples from developed countries and just 255 from developing countries. Appendix A also specifies the country from which the utility tariff was derived when the study applied one or more indirect valuation method.

Utility Catalogue

Appendix C lists the main sample mean or median utility or VAS scores, and their associated distributions, for the 1,191 main samples by their ICD-10 chapter, health condition, valuation method, respondent type and sample size. Information on populations from which the indirect valuation methods' tariffs were derived is provided at the bottom of the table. Appendix D provides the references for these tariffs.

Weighted Average Values

Table 3 outlines the results for the first part of the statistical analyses where weighted averages of main sample mean utility or VAS scores were calculated for each health condition category, by valuation method. Median utility or VAS scores were excluded from the analyses. The standard errors are reported in parentheses, whilst the ranges indicate the minimum and the maximum mean utility or VAS scores where applicable. The numbers of mean utility or VAS scores included in each analysis are presented in the second set of square brackets.

Meta-Regressions

Table 4 summarises the results of the meta-regression using HLM where only main samples that used the HUI3 were included, covering 279 samples across 89 studies and 76 health condition categories. The 0.876 constant represents the utility value for the baseline scenario, namely the weighted average of the mean HUI3 utility scores for general population samples, of minimum age less than 12 years from developed countries, with HRQoL self-assessed by children/adolescents using a self-administered survey in a health care or school setting. Health condition categories are included as indicator variables, and hence the coefficients for each condition category measures the decrement in mean HUI3 utility score from the baseline scenario. Using robust standard errors, 95% confidence intervals around the mean decrements can be calculated, as well as the associated p-values for statistical significance. For example, a utility decrement of 0.568 relative to baseline is provided for viral infections of the central nervous system (category 1.2), implying a mean utility score of 0.308 for this condition. The

health condition with the greatest utility decrement (excluding category 22 for combined chronic diseases) was category 21.3 for patients receiving palliative care (implied utility score of 0.017), followed by category 6.5 hydrocephalus (0.247) and category 17.4 congenital malformations of the nervous system (0.254). All categories containing cancer survivors (categories 2.1, 2.3, 2.7, 2.9, 2.10, 2.11 and 2.12) were associated with statistically significant utility *increments* relative to baseline, with the exception of brain tumour survivors (category 2.5), which showed a statistically significant HUI3 decrement of 0.074 ($P<0.001$). Survivors of successful kidney transplant (category 14.1) were also associated with a statistically significant HRQoL improvement relative to baseline (HUI3 utility score increment of 0.111; $P=0.016$). Laryngotracheal stenosis (category 10.3) and congenital diaphragmatic hernia (category 11.2) were the only other conditions which were associated with a statistically significant HUI3 increment. Overall, at the 5% significance level, 53 of 76 ICD-10 delineated health conditions were associated with statistically significant HUI3 decrements.

The meta-regression also suggests that different respondent types exerted significant effects (where a utility score difference of 0.03 is deemed to be clinically significant)⁵⁹ on health utility. Allowing children and/or adolescents to report their HRQoL together with their parents or caregivers led to an average decrement of 0.055 ($P<0.001$) in HUI3 score relative to when they report alone. Use of caregivers as proxies similarly led to an average decrement in utility score of 0.053 ($P<0.001$). In contrast, use of parents as proxies led to an overestimation of utility score (increment of 0.041; $P=0.001$) in comparison to the referent. Different modes of administration did not appear to exert statically significant effects on utility score relative to self-administration in a health care or school setting, except for telephone interview which resulted in a statically significant increment of 0.151 ($P<0.001$). Samples with a minimum age greater than 12 years (a proxy measure for adolescence) were associated with a statistically significant HUI3 decrement of 0.060 ($P=0.033$). Finally, children from developing countries reported a HUI3 decrement of 0.057, *ceteris paribus*, which was not statistically significant ($P=0.219$) despite the worse disease burden and healthcare environments they may face.

Table 5 summarises the meta-regression using HLM focussed on VAS-based approaches, covering 211 main samples across 67 studies and 57 health condition categories. The baseline scenario was associated with a VAS score of 82.88. As in Table 4, cancer survivorship (category 2.7) was associated with a better HRQoL than the baseline scenario (mean VAS increment of 12.58; $P<0.001$). Inflammatory and non-inflammatory disorders of the female pelvic organs (category 14.3) was the only other category associated with a significantly higher VAS score (mean increment of 7.52; $P=0.021$). Influenza and pneumonia (category 10.2), other

musculoskeletal disorders (13.4), imperforate anus (17.5) and survivors of other types of injuries (19.3) were associated with VAS increments which were not statistically significant at the 5% significance level. All other categories were associated with VAS decrements relative to the baseline scenario. At the 5% significance level, 38 of 57 ICD-10 delineated health conditions were associated with statistically significant VAS decrements.

Unlike the meta-regression for the HUI3, valuation of hypothetical health states was associated with a significant decrement in VAS score of 20.51 ($P<0.001$). Moreover, respondent type and mode of administration also exerted different influences on health outcome relative to the HUI3-based analysis. Assessment by children/adolescents together with parents or caregivers, and proxy-assessment by caregivers, were no longer associated with statistically significant underestimation of HRQoL. However, proxy-assessment by parents led to a statistically significant overestimation of HRQoL (VAS increment of 7.43; $P=0.005$), which was similar in relative magnitude and statistical significance to that revealed by the HUI3 analysis. Unlike for the HUI3, proxy-assessment by physicians or by the composite grouping of the general public, parents within the general public or adult patients resulted in a significant overestimation of the VAS score (for physicians: increment of 13.17; $P<0.001$; for composite group: 7.02; $P=0.008$). Furthermore, unlike for the HUI3, self-administered postal surveys were associated with an overestimation of VAS score relative to self-administration in health or school settings (increment of 4.63; $P=0.058$). Similarly, face-to-face interviews were associated with an overestimation of VAS score (increment of 5.99; $P=0.011$). As with the HUI3-based analyses, adolescents reported poorer HRQoL (VAS decrement of 5.45; $P=0.026$) relative to children under the age of 12. Similarly, children from developing countries reported poorer HRQoL (VAS decrement of 0.49), *ceteris paribus*, but this decrement was again not statistically significant.

DISCUSSION

This first comprehensive systematic review of primary studies reporting health utilities for childhood conditions and descriptors is substantially larger and broader in scope than previous reviews. It covers 272 studies as opposed to 90 studies by Thorrington and Eames³⁰ and 77 studies by Tarride and colleagues.²⁹ Earlier systematic reviews concentrated on specific health conditions, such as acute lymphoblastic leukaemia,^{28,46} or on specific valuation methods, such as the EQ-5D.⁴⁷ The study by Tarride and colleagues²⁹ was also limited to four valuation methods (EQ-5D, HUI, SG and TTO) and four health conditions (asthma, cancer, diabetes, skin diseases). In contrast, this study covers 19 valuation methods and 99 health conditions,

grouped by ICD-10 codes. In comparison, Petrou and Kupek³¹ covered 43 health conditions described by 2,236 parents of disabled children in the UK and valued solely using the HUI3; Carroll and Downs³² covered 27 hypothetical health conditions valued by 4,016 parents from the general US public; and Mittmann and colleagues³³ covered 19 health conditions experienced by 404 Canadian adolescents and valued solely using the HUI3. Moreover, this study is unique in detailing the characteristics of each of the included studies. The final catalogue of 1,191 mean or median utility or VAS scores corresponds in size to the largest published utility catalogues for adult populations, such as Tengs and Wallace's¹⁶ catalogue of 1,000 utility values. Furthermore, it is the only study that has applied a fixed-effects meta-analysis and mixed-effects meta-regression to health utilities in childhood populations. The primary analytical approach, namely hierarchical linear modelling, has to date only been applied in adult populations and for specific health conditions, such as colorectal cancers,²² HIV/AIDS²³ and breast cancer.²⁴ The studies by Tengs and Lin²³ and Peasgood and colleagues²⁴ similarly found that different respondent types exert independent effects on health utilities. These studies also share various limitations inherent in previous syntheses of utility values, such as unclear presentation of study characteristics (e.g. mode of administration) by primary sources,²² small data sets that restrict analyses of interaction effects between explanatory variables,²³ the use of main study samples only that exclude some sociodemographic (e.g. gender) or clinical factors (e.g. symptom type and severity) as covariables,^{22,24} and the use of published material only.²⁴

The finding from the meta-regression that 53 of 76 health condition categories were associated with statistically significant HUI3 decrements relative to general population health, after controlling for methodological factors, illustrates that this generic multi-attribute health classification instrument is sensitive to variations in health outcomes across a diverse range of disease areas in childhood health.⁶⁰ The finding that long-term survivors of childhood cancer enjoy better health-related quality of life compared to cancer patients, and in some instances compared to children in the general population, is consistent with findings in primary case-control studies (see for example Pogany and colleagues,⁶¹ and Apajasalo and colleagues⁶²), and illustrates the importance of conducting health utility measurements to provide an evidence-based justification for healthcare interventions in paediatric oncology.^{63,64} The VAS similarly seemed capable of detecting variations in health outcomes across conditions, associating survivorship of lymphoma (category 2.7) with a VAS increment relative to general population health and indicating a smaller VAS decrement for children born extremely preterm and without major comorbidity (category 16.1) than for those with major comorbidity (category

16.2), for example. It should be noted that the mixed effects meta-regression models test multiple hypotheses simultaneously, and caution is therefore required when drawing conclusions based on the *P*-values. Applying the Bonferroni correction to *P*-values would mean that only variables with *P*-values less than 0.00056 (0.05/89) for the HUI3 and 0.00071 (0.05/70) for the VAS can be interpreted as reflecting significant effects.⁶⁵ If a *P*-value less than 0.001 is adopted as the significance level, 50 out of 76 health condition categories for the HUI3 and 30 out of 57 for the VAS still exerted a significant impact on values relative to general population health. This suggests that the significant effects exerted by health conditions were not spurious results.

A number of methodological factors, including respondent type and mode of administration, were shown to have independent effects on both HUI3 and VAS scores after controlling for childhood health conditions. Of particular note was the finding that proxy assessment by parents is associated with an over-estimation of children's HRQoL outcomes, compared to those reported directly by children for both methods, although a more mixed pattern of results was found when other types of proxies were considered. Previous studies had found that parental-assessed VAS scores are poorly correlated with those provided by children with chronic arthritis;⁶⁶ that proxy-assessed HUI3 scores provided by caregivers are only moderately correlated with self-assessed scores provided by children with severe infections;⁶⁷ and that proxy-assessed HUI3 scores provided by parents are significantly higher than those provided directly by very-low birthweight adolescents.⁶⁸ A potential explanation for higher parental-proxy values may be that parents underestimate problems in less observable aspects of health such as emotional and social wellbeing, which may be acute in childhood.^{68,69} Furthermore, previous evidence revealed variation in the reporting of children's HRQoL outcomes by different types of proxies, for example, in the reporting of the HRQoL of young febrile children using a VAS by parents and physicians;⁷⁰ the reporting of the HRQoL of children with acute lymphoblastic leukemia, juvenile idiopathic arthritis or asthma using the HUI3 by parents and physicians;⁷¹ and the assessment of the HRQoL of extremely-low birthweight adolescents using SG by neonatologists and parents.⁷² With respect to mode of administration, the meta-regressions suggest that VAS measures of HRQoL outcomes were more significantly affected compared to the HUI3. These findings contradict those of Verrips and colleagues⁷³ who found that telephone interviews *underestimated* HUI3 utility scores for very-low birthweight children relative to self-administered paper questionnaires in health or school settings. Nevertheless, the results of meta-regressions should be seen as suggestive rather than definitive, and caution is required before interpreting them as accurate estimates of independent effects exerted by

various respondent types and modes of administration that can be generalised across all age groups and health conditions.

There are several caveats to the study results, which should be borne in mind by readers. First, our literature searches were limited to articles published online before 31st December 2015. Nevertheless, we are not aware of any more recent evidence that would have a qualitative impact on our study results. Second, although our search strategies were extensively piloted to maximise sensitivity, some eligible articles may have been missed. Third, information on the samples included in our analyses was extracted from published material. Several studies did not report important data relating to population characteristics, such as comorbidities, which would have entered our meta-regressions had they been available. Fourth, our selection of valuation methods was broad and encompassed methods, such as VAS variants, which arguably lack a theoretical basis for inclusion within cost-utility analysis.⁴⁹ Nevertheless, our approach is in keeping with previous systematic reviews of health utilities and permits the reader to select relevant values for their particular analysis.^{16,17}

A more fundamental caveat relates to the assumptions that needed to be made to allow for evidence synthesis. Exploring the impact on utility scores across variations in methodological factors required making potentially inappropriate assumptions about the comparability of the diverse collection of studies included in the evidence base. Factors such as respondent type, administration mode and target age may differ substantially between studies, potentially undermining the credibility and relevance of utility estimates derived by pooling across them. This could potentially be exacerbated by our use of ICD-10 codes for categorising samples, if there are conditions that are qualitatively different, and have different associated utilities, but fall under the same ICD-10 code. Hierarchical linear modelling thus relaxes the strong assumptions around comparability implied by fixed-effects meta-analysis in two ways. The first is meta-regression, in which a regression model controlling for confounding factors is embedded in the meta-analysis. The second is random (or mixed) effects meta-analysis, which relaxes the assumption that studies in similar populations are reporting the same underlying utilities, and allows for heterogeneity between such studies from unobserved factors. However, mixed-effects meta-regression does not completely eliminate problems associated with the comparability of studies within the evidence base. There were limited data on which to base meta-regression (in particular, we were unable to estimate utilities conditional on disease severity). Issues associated with aggregation of health conditions using ICD-10 codes remained. Whilst most health condition categories were classified using distinct ICD-10 codes, paucity of data for some categories compelled aggregation within or across ICD-10 sub-

chapters. More importantly, we were unable to estimate potential interactions between health conditions and methodological factors. It is possible, for example, that proxy-assessed values are more likely to be reported when respondents are younger, or have greater disease severity. This is a potential source of bias in our estimates of the impact of methodological factors on utility or VAS scores.

The number of economic evaluation of healthcare interventions in childhood populations has grown rapidly in recent decades, with cost-utility analysis seeing the fastest growth out of all evaluation techniques since 2009.⁷⁴ Future economic evaluations should benefit greatly from our catalogue of 1,191 mean or median utility or VAS scores and from our 3,414 sets of statistics in the accompanying Excel database. Moreover, the results of our meta-regressions ensure that the utility decrements associated with health conditions adequately control for a range of confounding factors. However, the valuation method selected for utility inputs is a key methodological variable, and further research based on our database should explore the independent effects of valuation methods (other than the HUI3) on health utilities. A past review by Finnell and colleagues⁷⁵ concludes that over one third of 39 paediatric cost-utility analyses found in the literature would reverse their result if utilities valued by SG or TTO were used rather than those valued by indirect valuation methods or expert opinion. Further research should also catalogue the effects of specific interventions or health programmes on health utility, as these are important inputs into decision analytic models.

In conclusion, this systematic review and meta-analysis of childhood utility values offers a wealth of resources to inform future economic evaluations within the childhood context. The fixed-effects approach offers a weighted average of health utilities and their distributions for health condition categories spanning all ICD-10 chapters relevant to childhood health, by valuation method. The mixed-effects meta-regression generates utility or VAS decrements for each condition relative to general population health after controlling for diverse methodological factors. Information within the appendices and the accompanying Excel database should act as a useful resource for analysts, as well as a basis for future methodological research studies.

ACKNOWLEDGMENTS

We would like to thank Samantha Johnson for her assistance with the development and piloting of the literature search strategies. The Warwick Clinical Trials Unit, University of Warwick, benefited from facilities funded through the Birmingham Science City Translational Medicine Clinical Research and Infrastructure Trials Platform, with support from Advantage West Midlands. The views contained within this paper are those of the authors and not necessarily of the funders.

SUPPLEMENTARY MATERIAL

Excel database containing information on all 3,414 sub-samples of health utilities and descriptors can be found online at <http://childhoodutilities.wordpress.com>. The website also contains the detailed search strategy and a guidance note for Excel navigation.

REFERENCES

1. Drummond MF, Sculpher MF, Claxton K, et al. *Methods for the Economic Evaluation of Health Care Programmes*, 4th edn.: Oxford University Press, 2015.
2. NICE. *NICE Guide to the Methods of Technology Appraisal*. London, UK: NICE, 2008.
3. Scottish Medicines Consortium (SMC). *Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF)*. Scotland: SMC, 2007.
4. Pharmaceutical Benefits Advisory Committee (PBAC). *Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee*. Australia: PBAC, 2002.
5. Canadian Agency for Drugs and Technologies in Health. *Guidelines for the economic evaluation of health technologies*: Canada. Ottawa: Canadian Agency for Drugs and Technologies in Health. 2006.
6. Torrance GW, Feeny D. Utilities and quality-adjusted life years. *Int J Technol Assess Health Care* 1989;5:559-75.
7. Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A. *Measuring and Valuing Health Benefits for Economic Evaluation*. Oxford, UK: Oxford University Press, 2007.
8. Dolan P, Gudex C, Kind P, Williams A. Valuing health states: a comparison of methods. *J Health Econ* 1996;15:209-31.
9. Brooks R. EQ-5D, the current state of play. *Health Pol* 1996;37:53-72.
10. Torrance GW, Furlong W, Feeny D, Boyle M. Multi-attribute preference functions: Health Utilities Index. *Pharmacoecon* 1995;7(6):503-20.
11. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21(2):271-92.
12. Kaplan RM, Bush JW, Berry CC. Health status: types of validity and the index of well-being. *Health Serv Res* 1976;11:478-507.
13. Hawthorne G, Richardson J, Osborne R. The Assessment of Quality of Life (AQoL) instrument: a psychometric measure of health-related quality of life. *Qual Life Res* 1999; 8: 209-24.
14. Brazier JE, Yang Y, Tsuchiya A, Rowen DL. A review of studies mapping (or cross walking) non-preference based measures of health to generic preference-based measures. *Eur J Health Econ* 2010;11(2):215-25.
15. Weinstein MC, O'Brien B, Hornberger J, Jackson J, Johannesson M, McCabe C, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. *Value Health* 2003;6(1):9-17.
16. Tengs TO, Wallace A. One thousand health-related quality-of-life estimates. *Med Care* 2000;38(6):583-637.
17. Bell CM, Chapman RH, Stone PW, Sandberg EA, Neumann PJ. An off-the-shelf help list: a comprehensive catalog of preference scores from published cost-utility analyses. *Med Decis Making* 2001;21:288-94.
18. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Making* 2008;28(4):582-92.
19. Doth AH, Hansson PT, Jensen MP, Taylor RS. The burden of neuropathic pain: a systematic review and meta-analysis of health utilities. *Pain* 2010;149(2):338-44.
20. Shearer J, Green C, Ritchie CW, Zajicek JP. Health state values for use in the economic evaluation of treatments for Alzheimer's disease. *Drugs Aging* 2012;29(1):31-43.
21. Mohiuddin S, Payne K. Utility values for adults with unipolar depression: Systematic review and meta-analysis. *Med Decis Making* 2014;34(5):666-85.

22. Djalalov S, Rabeneck L, Tomlinson G, Bremner KE, Hilsden R, Hoch JS. A review and meta-analysis of colorectal cancer utilities. *Med Decis Making* 2014;34(6):809-18.
23. Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. *Med Decis Making* 2002;22(6):475-81.
24. Peasgood T, Ward SE, Brazier J. Health-state utility values in breast cancer. *Expert Rev Pharmacoecon Outcomes Res* 2010;10(5):553-66.
25. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value Health* 2014;17(4):462-70.
26. Gheorghe A, Moran G, Duffy H, Roberts T, Pinkney T, Calvert M. Health utility values associated with surgical site infection: A systematic review. *Value Health* 2015;18(8):1126-37.
27. Malinowski KP, Kawalec P. Health utility of patients with Crohn's disease and ulcerative colitis: a systematic review and meta-analysis. *Expert Rev Pharmacoecon Outcomes Res* 2016;16(4):441-53.
28. van Litsenburg RR, Kunst A, Huisman J, Ket JC, Kaspers GJ, Gemke RJ. Health status utilities in pediatrics: a systematic review of acute lymphoblastic leukemia. *Med Decis Making* 2014;34(1):21-32.
29. Tarride JE, Burke N, Bischof M, Hopkins RB, Goeree L, Campbell K, Xie F, O'Reilly D, Goeree R. A review of health utilities across conditions common in paediatric and adult populations. *Health Qual Life Outcomes*. 2010;8:12.
30. Thorrington D, Eames K. Measuring health utilities in children and adolescents: a systematic review of the literature. *PloS One* 2015;10(8):e0135672.
31. Petrou S, Kupek E. Estimating preference-based Health Utilities Index Mark 3 utility scores for childhood conditions in England and Scotland. *Med Decis Making* 2009;29(3):291-303.
32. Carroll AE, Downs SM. Improving decision analyses: parent preferences (utility values) for pediatric health outcomes. *J Pediatr* 2009;155(1):21-5, 25 e1-5.
33. Mittmann N, Trakas K, Risebrough N, Liu BA. Utility scores for chronic conditions in a community-dwelling population. *Pharmacoeconomics* 1999;15(4):369-76.
34. Ungar WJ, Santos MT. The Pediatric Economic Database Evaluation (PEDE) Project: establishing a database to study trends in pediatric economic evaluation. *Med Care* 2003;41:1142-52.
35. Ungar WJ. The Pediatric Economic Database Evaluation (PEDE) Project. Toronto: The Hospital for Sick Children. 2016. Available from: <http://pede.ccb.sickkids.ca/pede/index.jsp>
36. Kromm SK, Bethell J, Kraglund F, Edwards SA, Laporte A, Coyte PC, Ungar WJ. Characteristics and quality of pediatric cost-utility analyses. *Qual Life Res*; 2012;21(8):1315-25.
37. Griebisch I, Coast J, Brown J. Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health. *Pediatrics* 2005;115(5):e600–14.
38. Petrou S. Methodological issues raised by preference-based approaches to measuring the health status of children. *Health Econ* 2003;12(8):697–702.
39. Ravens-Sieberer U, Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, Egmar AC, Gusi N, Herdman M, Jelsma J, Kind P, Olivares PR, Scalone L, Greiner W. Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study. *Qual Life Res* 2010;19(6):887-97.
40. Apajasalo M, Sintonen H, Holmberg C, Sinkkonen J, Aalberg V, Pihko H, Silmes MA, Kaitila I, Makela A, Rantakari K, Anttila R, Rautonen J. Quality of life in early

- adolescence: a sixteen-dimensional health-related measure (16D). *Qual Life Res* 1996;5(2):205-11.
41. Apajasalo M, Rautonen J, Holmberg C, Sinkkonen J, Aalberg V, Pihko H, Silmes MA, Kaitila I, Makela A, Erkkila K, Sintonen H. Quality of life in pre-adolescence: a 17-dimensional health-related measure (17D). *Qual Life Res* 1996;5(6):532-38.
 42. Richardson J, Peacock SJ, Hawthorne G, Iezzi A, et al. Construction of the descriptive system for the assessment of quality of life AQoL-6D utility instrument. *Health Qual Life Outcomes*. 2012;10:38-46.
 43. Stevens KJ. Working with children to develop dimensions for a preference-based, generic, pediatric health-related quality-of-life measure. *Qual Health Res* 2010;20:340-51.
 44. Chen G, Ratcliffe J. A review of the development and application of generic multi-attribute utility instruments for paediatric populations. *PharmocoEcon* 2015;33(10):1013-28.
 45. Moher D, Liberati A, Tetzlaff J, Altman DG, the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
 46. Pickard AS, Topfer LA, Feeny DH. A structured review of studies on health-related quality of life and economic evaluation in pediatric acute lymphoblastic leukemia. *Jour Nat Canc Inst Mono* 2004;33:102-25
 47. Noyes J, Edwards R. EQ-5D for the assessment of health-related quality of life and resource allocation in children: a systematic methodological review. *Value Health* 2011;14(8):1519-30.
 48. Janssens L, Gorter JW, Ketelaar M, Kramer WLM, Holtslag HR. Health-related quality-of-life measures for long-term follow-up in children after major trauma. *Qual Life Res* 2008;17:701-13.
 49. Parkin D, Devlin N. Is there a case for using visual analogue scale valuations in cost-utility analysis? *Health Econ* 2006;15(7):653-64.
 50. Sutton A, Abrams K, Jones D, et al. *Methods for meta-analysis in medical research*. John Wiley & Sons 2000.
 51. Richardson J, Khan MA, Iezzi A, Maxwell A. Comparing and explaining differences in the magnitude, content, and sensitivity of utilities predicted by the EQ-5D, SF-6D, HUI3, 15D, QWB, and AQoL-8D multiattribute utility instruments. *Med Dec Making* 2015;35(3):276-91.
 52. Juniper EF, Guyatt GH, Feeny DH, Griffith LE, Ferrie PJ. Minimum skills required by children to complete health-related quality of life instruments for asthma: comparison of measurement properties. *Eur Respir J* 1997;10:2285-94
 53. Oostenbrink R, Moll HA, Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. *Jour Clin Epid* 2002;55:791-99.
 54. Chiou C-F, Weaver MR, Bell MA, Lee TA, Krieger JW. Development of the multi-attribute Pediatric Asthma Health Outcome Measure (PAHOM). *Int J Qual Health Care* 2005;17(1):23-30.
 55. Lynch FL, Hornbrook M, Clarke GN, Perrin N, Polen MR, O'Connor E, Dickerson J. Cost-effectiveness of an intervention to prevent depression in at-risk teens. *Arch Gen Psychiatry* 2005;62:1241-48.
 56. Domino ME, Burns BJ, Silva SG, Kratochvil CJ, Vitiello B, Reinecke MA, Mario J, March JS. Cost-effectiveness of treatments for adolescent depression: results from TADS. *Am J Psychiatry* 2008;165:588-96.

57. Domino ME, Foster M, Vitiello B, Kratochvil CJ, Burns BJ, Silva SG, Reinecke MA, March JS. Relative cost-effectiveness of treatments for adolescent depression: 36-week results from the TADS randomised trial. *J Am Acad Child Adolesc Psychiatry* 2009;48(7):711-20
58. Lee D, Gladwell D, Batty AJ, Brereton N, Tate E. The cost effectiveness of licensed oromucosal midazolam (Buccolam()) for the treatment of children experiencing acute epileptic seizures: an approach when trial evidence is limited. *Paediatric Drugs* 2013;15(2):151-62
59. Grootendorst P, Feeny D, Furlong W. Health Utilities Index Mark 3 evidence of construct validity for stroke and arthritis in a population health survey. *Med Care* 2000;38(3):290-99.
60. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, et al. Multiattribute and single-attribute utility functions for the health utilities index mark 3 system. *Med care*. 2002;40(2):113-128.
61. Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, et al. Health status in survivors of cancer in childhood and adolescence. *Qual Life Res*. 2006;15(1):143-157.
62. Apajasalo M, Sintonen H, Siimes MA, Hovi L, Holmberg C, et al. Health-related quality of life of adults surviving malignancies in childhood. *Eur J Cancer* 1996;32(8):1354-8.
63. Barr RD, Furlong W, Dawson S, Whitton AC, et al. An assessment of global health status in survivors of acute lymphoblastic leukemia in childhood. *J Pediatr Hematol Oncol*. 1993;15(4):284-90.
64. Glaser AW, Furlong W, Walker DA, Fielding K, et al. Applicability of the Health Utilities Index to a population of childhood survivors of central nervous system tumours in the U.K. *Eur J Cancer*. 1999;35(2):256-61.
65. Bland M. An introduction to medical statistics, 3rd Edition. Oxford University Press, USA, 2000.
66. Brunner HI, Klein-Gitelman MS, Miller MJ, Trombley M, Baldwin N, et al. Health of children with chronic arthritis: relationship of different measures and the quality of parent proxy reporting. *Arthritis Rheum*. 2004;51(5):763-73.
67. Kulpeng W, Sornsrivichai V, Chongsuvivatwong V, Rattanaipapong W, Leelahavarong P, et al. Variation of health-related quality of life assessed by caregivers and patients affected by severe childhood infections. *BMC Pediatr*. 2013;13:122-30.
68. Wolke D, Chernova J, Eryigit-Madzwamuse S, Samara M, Zwierzynska K, et al. Self and parent perspectives on health-related quality of life of adolescents born very preterm. *J Pediatr*. 2013;163(4):1020-6 e2.
69. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. *Qual Life Res* 2001;10:347-57.
70. Kramer MS, Etezadi-Amoli J, Ciampi A, Tange SM, Drummond KN, et al. Parents' versus physicians' values for clinical outcomes in young febrile children. *Pediatrics*. 1994;93(5):697-702.
71. Janse AJ, Uiterwaal CSPM, Gemke RBJ, Kimpen JLL, Sinnema G. A difference in perception of quality of life in chronically ill children was found between parents and pediatricians. *J Clin Epidemiol*. 2005;58(5):495-502.
72. Saigal S, Stoskopf BL, Feeny D, Furlong W, Burrows E, et al. Differences in preferences for neonatal outcomes among health care professionals, parents, and adolescents. *JAMA*. 1999;281(21):1991-7.
73. Verrips GH, Stuifbergen MC, den Ouden AL, Bonsel GJ, Gemke RJ, et al. Measuring health status using the Health Utilities Index: agreement between raters and between modalities of administration. *J Clin Epidemiol*. 2001;54(5):475-81.

74. Sullivan S, Ungar WJ. Full report: Will the growth spurt continue? Trends in child health economic evaluation: 1980 to 2013. 2016.
75. Finnell SME, Carroll AE, Downs SM. Application of classic utilities to published pediatric cost-utility studies. *Academic Ped* 2012;12(3):219-28.

Table 1: Number of samples by ICD-10 chapter and health condition category

Health Condition Category	Health Condition Sub-Category	ICD-10 Code	Number of Samples*
General population and control group			
0. All samples			409 (112)**
ICD-10 Chapter 1: Infectious and parasitic diseases			192 (87)
1.1 Gastroenteritis	Rotavirus gastroenteritis	1-A08	27 (12)
	Non-rotavirus gastroenteritis	1-A09	22 (6)
1.2 Viral infections of central nervous system	Viral meningitis caused by viral fever	1-A87	3 (3)
	Combined sample of central nervous system infection (meningitis, encephalitis)	1-A86-A87	2 (1)
1.3 Meningococcal infection without permanent sequelae	Bacterial meningococcal meningitis	1-A39	13 (5)
1.4 Meningococcal infection with permanent sequelae	Bacterial meningococcal meningitis	1-A39	42 (23)
	Meningococcal sepsis	1-A39.2	3 (3)
	Severe meningitis (viral or bacterial unspecified)	1-A39	8 (8)
1.5 Pertussis		1-A37	28 (10)
1.6 Viral fever		1-A99	30 (6)
1.7 Bacteremia		1-A49	8 (8)
1.8 Human immunodeficiency virus		1-B20	4 (2)
1.9 Chickenpox		1-B01	2 (0)
ICD-10 Chapter 2: Cancer			432 (150)
2.1 Survivors of combined types of cancer		2	87 (24)
2.2 Patients of combined types of cancer on active therapy	Combined types of cancer	2	60 (19)
	Recurrent juvenile-onset respiratory papillomatosis	2-D14.1	2 (2)
2.3 Survivors of acute lymphoblastic leukaemia		2-C91	46 (22)
2.4 Patients of acute lymphoblastic leukaemia on active therapy		2-C91	39 (14)
2.5 Survivors of brain tumour	Combined types of brain tumour	2-C71	105 (29)
	Medulloblastoma	2-C71.6	15 (1)
2.6 Patients of brain tumour on active therapy		2-C71	4 (1)
2.7 Survivors of lymphoma	Combined types of lymphoma	2-C81-C85	1 (1)
	Hodgkin's disease	2-C81	16 (11)
	Non-Hodgkin's lymphoma	2-C82-C85	4 (2)
2.8 Patients of lymphoma on active therapy	Hodgkin's disease	2-C81	18 (3)
2.9 Survivors of renal tumour	Combined types of renal tumour	2-C64	5 (3)
	Wilms' tumour	2-C64	4 (4)
2.10 Survivors of retinoblastoma		2-C69.2	3 (3)
2.11 Survivors of sympathetic nervous system tumour	Combined types of sympathetic nervous system tumour	2-C74.9	1 (1)
	Neuroblastoma	2-C74.9	6 (4)
2.12 Survivors of other types of cancer	Germ cell tumour	2-C62	2 (2)

	Bone tumour	2-C41	5 (1)
	Hepatic tumour	2-C22.2	3 (1)
	Soft tissue sarcoma	2-C49	3 (1)
	Carcinoma	2-D00	1 (1)
	Teratoma	2-C62.9	2 (0)
ICD-10 Chapter 3: Diseases of the blood and immune system			73 (19)
3.1 Haemophilia		3-D66	63 (14)
3.2 Haemolytic anaemias	Sickle cell disease	3-D57	4 (2)
	Favism	3-D55	2 (1)
	Thalassemia	3-D56	2 (1)
3.3 Combined diseases of the blood		3	2 (1)
ICD-10 Chapter 4: Endocrine, nutritional and metabolic disorders			362 (95)
4.1 Overweight		4-E66	162 (18)
4.2 Obese or Diabetes type II	Obese	4-E66	23 (11)
	Diabetes type II	4-E11	28 (1)
4.3 Diabetes type I		4-E10	41 (22)
4.4 Cystic fibrosis		4-E84	63 (21)
4.5 Congenital adrenal hyperplasia		4-E25	12 (4)
4.6 Hypophosphatasia		4-E83.3	6 (4)
4.7 Phenylketonuria		4-E70	5 (3)
4.8 Other metabolic disorders	Glutaricaciduria type 1	4-E72	3 (2)
	Long-chain acyl-CoA dehydrogenase deficiency (LCHADD)	4-E71	5 (2)
	Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)	4-E71	5 (2)
	Galactosemia	4-E74.2	2 (1)
	Mucopolysaccharidosis	4-E76	1 (1)
	Mucopolysaccharidosis type II (Hunter Syndrome)	4-E76.1	1 (1)
	Hypothyroidism	4-E03	2 (1)
	Combined metabolic disorders	4	3 (1)
ICD-10 Chapter 5: Mental and behavioural disorders			537 (142)
5.1 Attention-deficit hyperactivity disorder		5-F90	153 (48)
5.2 Autism spectrum disorder		5-F84	7 (6)
5.3 Pervasive developmental disorders other than autism spectrum disorder	Asperger's disorder	5-F84.5	2 (2)
	Combined pervasive developmental disorders	5-F84	136 (4)
5.4 Depression	Depression	5-F32	58 (10)
	Major depressive disorder	5-F33	1 (1)
	Dysthymic disorder	5-F34	1 (1)
5.5 Behavioural disorders	Combined behavioural disorder	5-F91	4 (3)
	Tic disorder	5-F95	2 (2)
	Movement disorder	5-F98	1 (1)
	Enuresis	5-F98	1 (1)
5.6 Stress-related and somatoform disorders	Combined anxiety disorders (onset in childhood and adolescence)	5-F93	18 (4)
	Social phobia	5-F93.2	1 (1)
	Internalising disorder	5-F93	12 (1)
	Specific phobia	5-F40.2	1 (1)
	Panic disorder	5-F41	1 (1)

	Agoraphobia	5-F40	1 (1)
	Generalised anxiety disorder	5-F41.1	1 (1)
	Obsessive compulsive disorder	5-F42	1 (1)
	Post-traumatic stress disorder	5-F43.1	5 (2)
	Conversion disorder	5-F44	1 (1)
	Hypochondriasis	5-F45.2	1 (1)
	Victims of bullying	5	7 (3)
5.7 Personality disorders	Borderline personality disorder	5-F60.3	1 (1)
	Avoidant personality disorder	5-F60.6	1 (1)
	Obsessive-compulsive personality disorder	5-F60.5	1 (1)
	Depressive personality disorder	5-F60	1 (1)
	Personality disorder, not otherwise specified	5-F60	9 (1)
5.8 Other mental disorders	Combined psychiatric disorders (diagnosed by DSM-IV)	5	6 (1)
	Combined mental disorders	5	25 (2)
	Risk of psychosis	5-F20	6 (2)
5.9 Disorders of speech and language	Receptive language disorder	5-F80.2	2 (2)
	Combined speech disorders	5-F80.9	4 (2)
	Stuttering	5-F98.5	20 (2)
5.10 Disorders of scholastic skills	Learning disabilities	5-F81	8 (6)
	Dyslexia	5-F81	1 (1)
5.11 Cognitive impairment		5-F06	8 (4)
5.12 Mental retardation	Mental retardation	5-F72	18 (10)
	Motor disorder	5-F82	2 (1)
5.13 Eating disorders		5-F50	3 (3)
5.14 Substance use disorders		5-F10	5 (4)
ICD-10 Chapter 6: Nervous system disorders			96 (45)
6.1 Cerebral palsy		6-G80	31 (9)
6.2 Muscular dystrophy	Duchenne muscular dystrophy	6-G71	15 (6)
	Muscular dystrophy and Spinal muscular atrophy	6-G71/G12	2 (1)
6.3 Epilepsy		6-G40	27 (15)
6.4 Migraine		6-G43	5 (3)
6.5 Hydrocephalus		6-G91	8 (7)
6.6 Combined disorders of the nervous system	Neurodevelopmental impairment	6-G96	6 (3)
	Combined rare disorders of the central nervous system	6-G96	2 (1)
ICD-10 Chapter 7: Diseases of the eye			61 (9)
7.1 Visual disturbances and blindness		7-H54	10 (3)
7.2 Other diseases of the eye	Combined diseases of the eye	7	4 (1)
	Nystagmus	7-H55	1 (1)
	Visual pathway impairment	7-H47	1 (1)
	Cataracts	7-H26	1 (1)
	Myopia	7-H52.1	44 (2)
ICD-10 Chapter 8: Diseases of the ear			156 (55)
8.1 Moderate hearing loss		8-H90	56 (19)
8.2 Severe hearing loss	Severe hearing impairment	8-H90	49 (16)
	Deafness	8-H91	4 (2)
8.3 Acute otitis media		8-H66	16 (14)
8.4 Otitis media with effusion		8-H65.9	31 (4)
ICD-10 Chapter 9: Circulatory system disorders			16 (15)

9.1 Hypertension		9-I10	4 (4)
9.2 Stroke		9-I64	5 (5)
9.3 Heart disease	Cardiovascular disease	9-I51	3 (2)
	Heart failure (awaiting heart transplant)	9-I50	2 (2)
	Heart failure (after successful heart transplant)	9-I50	2 (2)
ICD-10 Chapter 10: Respiratory system disorders			175 (59)
10.1 Chronic lower respiratory disease	Asthma	10-J45	127 (25)
	Bronchitis and Emphysema	10-J40/J43	1 (1)
10.2 Influenza and pneumonia	Pneumonia	10-J12	11 (11)
	Influenza A/H1N1	10-J09	1 (0)
10.3 Laryngotracheal stenosis		10-J38.6	9 (7)
10.4 Upper respiratory infections and diseases	Tonsillitis	10-J03	14 (4)
	Sinusitis	10-J01	1 (1)
	Rhinitis	10-J30	1 (1)
10.5 Combined disorders of respiratory system	Combined lung disease	10-J96	8 (8)
	Combined respiratory system disorders	10	2 (1)
ICD-10 Chapter 11: Digestive system disorders			52 (15)
11.1 Noninfective enteritis and colitis	Crohn's disease and Ulcerative colitis	11-K50-K51	20 (6)
	Ulcerative colitis	11-K51	2 (1)
	Food hypersensitivity	11-K52.2	1 (1)
11.2 Congenital diaphragmatic hernia		11-K44	2 (2)
11.3 Dental caries		11-K02	10 (1)
11.4 Other disorders of the digestive system	Liver failure (awaiting liver transplant)	11-K72	1 (1)
	Combined liver diseases	11-K76	3 (1)
	Combined digestive disorders	11	2 (1)
	Gastric ulcer	11-K25	1 (1)
11.5 Celiac disease		11-K90	10 (0)
ICD-10 Chapter 12: Diseases of the skin			26 (8)
12.1 Atopic dermatitis		12-L20	16 (5)
12.2 Acne		12-L70	8 (2)
12.3 Combined skin diseases		12	2 (1)
ICD-10 Chapter 13: Musculoskeletal system disorders			63 (21)
13.1 Juvenile idiopathic arthritis		13-M08	15 (6)
13.2 Scoliosis		13-M41	7 (3)
13.3 Hip dysplasia	Developmental hip dysplasia	13-M87	1 (1)
	Legg-Calve-Perthes disease	13-M91.1	1 (1)
	Unilateral slipped capital femoral epiphysis	13-M91.1	2 (2)
13.4 Combined musculoskeletal disorders	Combined disorders	13	32 (7)
	Back pain	13-M54	1 (1)
ICD-10 Chapter 14: Genitourinary system disorders			55 (35)
14.1 Kidney failure (after successful kidney transplant)		14-N17	8 (6)
14.2 Kidney disease (before kidney transplant or after failed transplant)		14-N18	17 (6)

14.3 Inflammatory and non-inflammatory disorders of female pelvic organs	Pelvic inflammatory disease	14-N73	20 (16)
	Endometriosis	14-N80	4 (2)
14.4 Other urogenital disorders	Combined urogenital disorders	14	2 (1)
	Urinary tract infection	14-N39	3 (3)
	Urinary incontinence	14-N39.3	1 (1)
ICD-10 Chapter 16: Conditions originating in the perinatal period			201 (93)
16.1 ELBW/EPT without major comorbidity		16-P07	101 (48)
16.2 ELBW/EPT with major comorbidity		16-P07	69 (36)
16.3 VLBW/VPT		16-P07.1	22 (7)
16.4 Foetal alcohol spectrum disorder		16-P04.3	9 (2)
ICD-10 Chapter 17: Congenital malformations			85 (40)
17.1 Spina bifida		17-Q05	30 (9)
17.2 Craniosynostosis	Apert syndrome	17-Q87	2 (2)
	Crouzon syndrome	17-Q75.1	2 (2)
	Muenke syndrome	17-Q75	2 (2)
	Saethre-Chotzen syndrome	17-Q75	2 (2)
	Combined craniosynostosis	17-Q75	4 (2)
17.3 Other congenital limb, bone and facial deformities	Combined skeletal dysplasia	17-Q77	4 (2)
	Achondroplasia	17-Q77.4	1 (1)
	Congenital scoliosis	17-Q76.3	3 (1)
	Combined bone deformities	17-Q77	2 (1)
	Osteogenesis imperfecta and other bone deformities	17-Q78	2 (1)
	Congenital skeletal and facial conditions	17-Q79	2 (1)
	Congenital conditions of the connective tissue	17-Q68	2 (1)
	Arthrogryposis multiple congenital	17-Q74.3	1 (1)
	Combined lower limb deformities	17-Q72.9	1 (1)
17.4 Congenital malformations of the nervous system	Microcephaly	17-Q02	2 (1)
	Chiari type I malformation	17-Q07	4 (1)
17.5 Imperforate anus		17-Q42.3	8 (3)
17.6 Chromosomal abnormalities	Fragile X syndrome	17-Q99.2	3 (2)
	Down syndrome	17-Q90	2 (1)
	Williams syndrome	17-Q93.8	2 (1)
	Combined syndromes	17-Q99	4 (2)
ICD-10 Chapter 19: Injury, poisoning and other consequences of external causes			295 (36)
19.1 Survivors of combined types of injuries		19	148 (18)
19.2 Survivors of head and facial injuries	Combined head injuries	19-S00-S09	98 (4)
	Facial injury	19-S04.5	4 (1)
19.3 Survivors of other types of injuries	Burns	19-T20-T32	7 (2)
	Upper extremity fractures	19-S60-S69	4 (1)
	Lower extremity fractures	19-S80-S89	4 (1)
	Extremity dislocation	19	4 (1)
	Internal organ injury	19-T06.5	4 (1)
	Lead poisoning	19-T56	1 (1)
19.4 Allergy	Food allergy	19-T78	8 (2)
	Combined types of allergy	19-T78.4	13 (4)
ICD-10 Chapter 21: Contact with health services			52 (11)

21.1 Survivors of paediatric intensive care for unspecified reasons	21	43 (7)
21.2 Unspecified organ failure awaiting transplant	21	7 (2)
21.3 Palliative care	21	2 (2)
<hr/>		
Combined chronic diseases		
22. Combined types of chronic diseases		76 (26)
	Total:	3,414 (1,073)

*Number of samples from whole database (Number of main sample mean utility or VAS scores, excluding main sample median scores). **Number of main samples of mean or median scores are: General population and control group (119); Chapter 1 (91); Chapter 2 (206); Chapter 3 (19); Chapter 4 (119); Chapter 5 (142); Chapter 6 (47); Chapter 7 (9); Chapter 8 (61); Chapter 9 (15); Chapter 10 (59); Chapter 11 (26); Chapter 12 (8); Chapter 13 (21); Chapter 14 (35); Chapter 16 (100); Chapter 17 (40); Chapter 19 (36); Chapter 21 (12); Combined chronic diseases (28); with 1,186 main samples in total. ELBW/EPT: Extremely-low birthweight or extremely preterm birth. VLBW/VPT: Very-low birthweight or very preterm birth.

Table 2: Characteristics of all samples (main samples) by valuation method, respondent type, mode of administration, age of children and country of origin

Number of samples (main samples) by valuation method					
Direct valuation methods					
VAS: 212 (118)	EQ-5D VAS: 231 (71)	EQ-5D-Y VAS: 158 (58)	TTO: 137 (57)	SG: 221 (100)	Chained Gamble: 143 (38)
Indirect valuation methods					
QWB: 218 (15)	15D/16D/17D: 114 (52)	EQ-5D: 342 (124)	EQ-5D-Y: 68 (9)	AQoL-5D: 16 (4)	AQoL-6D: 41 (7)
CHU9D: 188 (22)	HUI2: 460 (195)	HUI3: 768 (300)	Modified HUI: 8 (5)	SF-6D: 13 (7)	PAHOM: 69 (5)
Utility from NPB: 7 (4)					
Number of samples (main samples) by respondent type					
Self-assessment by children and/or adolescents: 1,181 (349)		Assessment by children/adolescents and parents: 332 (112)		Assessment by children/adolescents and caregivers: 63 (39)	
Proxy assessment by parents: 997 (408)		Proxy assessment by caregivers: 429 (110)		Proxy assessment by physicians: 196 (100)	
Proxy assessment by physicians and caregivers: 29 (1)		Proxy assessment by nurses: 76 (26)		Proxy assessment by the general public: 20 (10)	
Proxy assessment by parents from the general public: 77 (35)		Proxy assessment by adult patients: 7 (1)		Proxy assessment by parents, adult patients and the general public: 7 (0)	
Number of samples (main samples) by mode of administration					
Self-administration by respondents					
Non-postal survey: 944 (297)		Postal survey: 762 (239)		Online survey: 255 (51)	
Delphi process: 5 (1)					
Interview-administration					
Face-to-face interview: 1,166 (523)		Telephone interview: 232 (51)		Face-to-face or telephone: 15 (5)	
Mode of administration not specified: 35 (24)					
Number of samples (main samples) by minimum age of children					
Minimum age of 0: 220 (96)		Minimum age of 2: 246 (37)		Minimum age of 5: 515 (161)	
Minimum age of 8: 875 (258)		Minimum age of 12: 693 (305)		Minimum age of 15: 349 (137)	
Minimum age of 18: 9 (6)		Age unspecified: 508 (191)			
Number of samples (main samples) by country					
Argentina: 2 (2)	Australia: 238 (37)	Austria: 12 (3)	Belgium: 2 (0)	Brazil: 5 (3)	Bulgaria: 2 (2)
Canada: 575 (283)	China: 24 (2)	Columbia: 12 (4)	Cuba: 16 (0)	Denmark: 10 (4)	Finland: 114 (52)
France: 3 (3)	Germany: 36 (18)	Honduras: 8 (0)	Hungary: 2 (2)	India: 2 (2)	Iran: 8 (4)
Italy: 23 (17)	Netherlands: 336 (109)	New Zealand: 14 (3)	Portugal: 2 (1)	Russia: 8 (6)	Singapore: 44 (2)
South Africa: 43 (8)	Sweden: 131 (50)	Thailand: 71 (66)	Turkey: 6 (5)	UK: 553 (193)	Uruguay: 12 (3)
US: 918 (213)	Zimbabwe: 4 (2)	Developed countries: 141 (65)	Developed and developing: 1 (1)	South America: 30 (24)	Not specified: 6 (2)

Table 3: Weighted averages of mean utility or VAS scores for each health condition category, by valuation method

General population and control group				
0. All samples	[VAS] 91.8 (1.77) 73.3-92.7 [4]	[EQ-5D VAS] 93.4 (2.69) 74.6- 96.0 [5]	[EQ-5D-Y VAS] 86.8 (1.19) 77.3- 96.0 [20]	[TTO] 0.982 (0.022) 0.839- 0.985 [2] [15D/16D/17D] 0.947 (0.004) 0.933-0.989 [10]
	[SG] 0.976 (0.011) 0.930- 0.984 [3]	[CG] 0.930 (0.010) [1]	[QWB] 0.875 (0.001) [1]	[AQoL-6D] 0.855 (0.021) 0.743- 0.890 [4] [SF-6D] 0.760 (0.007) [1]
	[EQ-5D] 0.948 (0.013) 0.880- 0.960 [5]	[EQ-5D-Y] 0.875 (0.011) 0.720- 0.889 [5]	[AQoL-5D] 0.870 (0.005) [1]	
	[CHU9D] 0.840 (0.012) 0.750- 0.931 [13]	[HUI2] 0.913 (0.012) 0.853- 0.960 [13]	[HUI3] 0.916 (0.010) 0.800- 0.970 [24]	
ICD-10 Chapter 1: Infectious and parasitic diseases				
1.1 Gastroenteritis	[VAS] 50.0 (1.54) 41.8-50.3 [2]	[EQ-5D VAS] 54.8 (1.94) [1]	[TTO] 0.931 (0.010) 0.920- 0.940 [2]	[CG] 0.918 (0.015) 0.900- 0.930 [2]
	[EQ-5D] 0.581 (0.041) -0.208- 0.634 [9]	[HUI2] 0.865 (0.064) 0.735- 0.896 [2]		
1.2 Viral infections of central nervous system	[VAS] 48.1 (3.45) 44.7-56.3 [3]	[HUI3] 0.174 (0.076) [1]		
1.3 Meningococcal infection without permanent sequelae	[CG] 0.995 (0.002) 0.977- 0.997 [4]	[HUI2] 0.930 (0.009) [1]		
1.4 Meningococcal infection with permanent sequelae	[VAS] 57.8 (9.92) 41.5-85.4 [4]	[EQ-5D VAS] 47.3 (1.88) 46.0- 50.0 [2]	[CG] 0.738 (0.123) 0.390- 0.861 [3]	[EQ-5D] 0.739 (0.052) 0.020- 0.830 [6]
	[HUI2] 0.797 (0.041) 0.520- 0.880 [8]	[HUI3] 0.550 (0.092) 0.240- 0.820 [7]	[Modified HUI] 0.593 (0.076) 0.440-0.780 [4]	
1.5 Pertussis	[TTO] 0.777 (0.068) 0.330- 0.930 [10]			
1.6 Viral fever	[VAS] 61.6 (2.03) 55.1-68.5 [6]			
1.7 Bacteremia	[EQ-5D VAS] 60.0 (1.41) 58.0- 61.0 [2]	[EQ-5D] 0.368 (0.018) 0.340- 0.380 [2]	[HUI2] 0.628 (0.034) 0.610- 0.690 [2]	[HUI3] 0.538 (0.026) 0.480- 0.550 [2]
1.8 Human immunodeficiency virus	[EQ-5D] 0.682 (0.070) 0.612- 0.752 [2]			
ICD-10 Chapter 2: Cancer				
2.1 Survivors of combined types of cancer	[15D/16D/17D] 0.950 (0) 0.950- 0.950 [2]	[HUI2] 0.938 (0.008) 0.870- 0.970 [15]	[HUI3] 0.902 (0.025) 0.730- 0.950 [7]	
2.2 Patients of combined types of cancer on active therapy	[VAS] 80.1 (5.00) 75.0-85.0 [2]	[TTO] 0.640 (0.055) [1]	[SG] 0.694 (0.057) 0.670- 0.830 [2]	[CG] 0.920 (0.038) [1]
	[QWB] 0.802 (0.029) [1]	[HUI2] 0.773 (0.028) 0.650- 0.840 [6]	[HUI3] 0.693 (0.028) 0.478- 0.760 [8]	
2.3 Survivors of acute lymphoblastic leukaemia	[HUI2] 0.956 (0.009) 0.871- 0.980 [11]	[HUI3] 0.888 (0.014) 0.722- 0.950 [11]		
2.4 Patients of acute lymphoblastic leukaemia on active therapy	[EQ-5D-Y VAS] 78.8 (2.81) 76.9- 83.0 [2]	[HUI2] 0.792 (0.032) 74.0-86.0 [4]	[HUI3] 0.809 (0.040) 66.0-91.0 [8]	
2.5 Survivors of brain tumour	[HUI2] 0.857 (0.014) 0.630- 0.940 [22]	[HUI3] 0.744 (0.018) 0.601- 0.830 [8]		

2.6 Patients of brain tumour on active therapy	[HUI3] 0.530 (0.067) [1]			
2.7 Survivors of lymphoma	[EQ-5D VAS] 90.0 (2.40) [1]	[HUI2] 0.873 (0.015) 0.820- 0.930 [7]	[HUI3] 0.857 (0.018) 0.720- 0.940 [6]	
2.8 Patients of lymphoma on active therapy	[EQ-5D VAS] 61.0 (2.44) [1]	[HUI2] 0.670 (0.024) [1]	[HUI3] 0.580 (0.024) [1]	
2.9 Survivors of renal tumour	[HUI2] 0.946 (0.004) 0.930- 0.950 [4]	[HUI3] 0.911 (0.014) 0.890- 0.930 [3]		
2.10 Survivors of retinoblastoma	[HUI2] 0.883 (0.067) [1]	[HUI3] 0.858 (0.007) 0.830- 0.860 [2]		
2.11 Survivors of sympathetic nervous system tumour	[HUI2] 0.895 (0.006) 0.880- 0.900 [3]	[HUI3] 0.878 (0.004) 0.870- 0.880 [2]		
2.12 Survivors of other types of cancer	[HUI3] 0.833 (0.021) 0.490- 0.870 [5]			
ICD-10 Chapter 3: Diseases of the blood and immune system				
3.1 Haemophilia	[VAS] 30.9 (4.33) 23.7-38.7 [3]	[EQ-5D VAS] 89.1 (5.60) 80.7- 92.8 [2]	[SG] 0.701 (0.072) 0.487- 0.915 [6]	[EQ-5D] 0.647 (0.208) -0.110- 0.780 [3]
3.2 Haemolytic anaemias	[EQ-5D VAS] 87.0 (3.60) [1]	[TTO] 0.793 (0.045) [1]	[EQ-5D] 0.905 (0.038) 0.590- 0.910 [2]	
3.3 Combined diseases of the blood	[HUI3] 0.505 (0.089) [1]			
ICD-10 Chapter 4: Endocrine, nutritional and metabolic disorders				
4.1 Overweight	[EQ-5D VAS] 78.4 (0.464) [1]	[EQ-5D-Y VAS] 78.5 (1.79) 74.6- 86.1 [4]	[EQ-5D-Y] 0.853 (0.045) 0.670- 0.890 [3]	[AQoL-6D] 0.852 (0.013) 0.842- 0.870 [2]
	[CHU9D] 0.844 (0.013) 0.810- 0.860 [4]	[HUI2] 0.841 (0.019) 0.838- 0.950 [2]	[HUI3] 0.786 (0.001) 0.780- 0.786 [2]	
4.2 Obese or Diabetes type II	[EQ-5D VAS] 73.2 (1.78) 69.1- 74.0 [2]	[EQ-5D-Y VAS] 81.9 (4.48) 75.4- 88.1 [3]	[EQ-5D] 0.790 (0.025) [1]	[AQoL-6D] 0.805 (0.011) [1]
	[CHU9D] 0.828 (0.001) 0.827- 0.830 [2]	[HUI2] 0.814 (0.009) [1]	[HUI3] 0.820 (0.099) 0.759- 0.980 [2]	
4.3 Diabetes type I	[EQ-5D VAS] 80.7 (0.147) 80.5- 80.8 [2]	[TTO] 0.809 (0.019) 0.530- 0.840 [7]	[SG] 0.933 (0.020) 0.744- 0.965 [6]	[EQ-5D] 0.905 (0.015) 0.765- 0.920 [4]
	[HUI3] 0.902 (0.027) 0.572- 0.910 [3]			
4.4 Cystic fibrosis	[VAS] 76.0 (2.48) [1]	[EQ-5D VAS] 77.1 (1.61) [1]	[EQ-5D-Y VAS] 82.2 (2.99) 79.4- 85.4 [2]	[TTO] 0.959 (0.017) 0.700- 0.960 [2]
	[SG] 0.920 (0.019) [1]	[QWB] 0.766 (0.025) 0.611- 0.790 [5]	[EQ-5D] 0.783 (0.021) [1]	[HUI2] 0.830 (0.003) 0.800- 0.850 [4]
	[HUI3] 0.743 (0.009) 0.728- 0.770 [4]			
4.5 Congenital adrenal hyperplasia	[15D/16D/17D] 0.853 (0.030) 0.780-0.920 [4]			
4.6 Hypophosphatasia	[EQ-5D] 0.410 (0.258) -0.240- 0.860 [4]			
4.7 Phenylketonuria	[TTO] 0.397 (0.039) [1]	[15D/16D/17D] 0.610 (0.030) 0.580-0.640 [2]		

4.8 Other metabolic disorders	[TTO] 0.472 (0.003) 0.469- 0.475 [2]	[15D/16D/17D] 0.643 (0.070) 0.490-0.890 [6]	[EQ-5D] 0.070 (0.019) [1]	[HUI3] 0.504 (0.025) 0.389- 0.510 [2]
ICD-10 Chapter 5: Mental and behavioural disorders				
5.1 Attention-deficit hyperactivity disorder	[VAS] 48.3 (5.88) 26.1-73.9 [8] [CG] 0.812 (0.038) 0.480- 0.920 [11]	[EQ-5D VAS] 54.8 (7.83) 30.2- 72.4 [5] [EQ-5D] 0.798 (0.012) 0.740- 0.810 [4]	[TTO] 0.833 (0.105) 0.444- 0.900 [3] [HUI2] 0.802 (0.020) 0.792- 0.896 [3]	[SG] 0.917 (0.007) 0.880- 0.960 [10] [HUI3] 0.664 (0.034) 0.425- 0.690 [4]
5.2 Autism spectrum disorder	[EQ-5D-Y VAS] 80.7 (0.024) [1]	[QWB] 0.580 (0.015) [1]	[HUI2] 0.721 (0.046) [1]	[HUI3] 0.629 (0.037) 0.431- 0.700 [4]
5.3 Pervasive developmental disorders other than autism spectrum disorder	[QWB] 0.595 (0.007) 0.591- 0.620 [3]	[HUI3] 0.674 (0.041) 0.659- 0.790 [2]		
5.4 Depression	[EQ-5D VAS] 57.0 (2.00) 55.0- 59.0 [2]	[EQ-5D] 0.892 (0.038) 0.450- 0.910 [6]	[NPB] 0.570 (0.035) 0.162- 0.869 [4]	
5.5 Behavioural disorders	[EQ-5D-Y VAS] 76.9 (3.49) [1]	[EQ-5D] 0.250 (0.183) [1]	[HUI2] 0.802 (0.0003) 0.801- 0.802 [2]	[HUI3] 0.620 (0.089) 0.463- 0.727 [3]
5.6 Stress-related and somatoform disorders	[EQ-5D VAS] 76.2 (1.99) [1] [HUI3] 0.706 (0.012) 0.672- 0.710 [2]	[EQ-5D] 0.701 (0.056) 0.250- 0.830 [10] [SF-6D] 0.708 (0.004) 0.690- 0.710 [3]	[AQoL-5D] 0.710 (0.028) [1]	[HUI2] 0.760 (0.040) [1]
5.7 Personality disorders	[EQ-5D] 0.499 (0.046) 0.340- 0.700 [5]			
5.8 Other mental disorders	[15D/16D/17D] 0.797 (0.002) 0.795-0.799 [2]	[CHU9D] 0.778 (0.031) 0.739- 0.803 [2]	[HUI3] 0.698 (0.039) [1]	
5.9 Disorders of speech and language	[EQ-5D VAS] 88.3 (0.969) [1]	[15D/16D/17D] 0.941 (0.007) 0.934-0.948 [2]	[HUI3] 0.878 (0.041) 0.438- 0.890 [3]	
5.10 Disorders of scholastic skills	[VAS] 54.6 (2.92) 51.6-61.5 [3]	[EQ-5D-Y VAS] 79.4 (3.02) [1]	[EQ-5D] 0.770 (0.018) [1]	[HUI3] 0.397 (0.020) 0.376- 0.417 [2]
5.11 Cognitive impairment	[HUI2] 0.738 (0.049) 0.612- 0.757 [2]	[HUI3] 0.592 (0.118) 0.318- 0.643 [2]		
5.12 Mental retardation	[EQ-5D VAS] 56.0 (0.020) 55.0- 60.0 [2] [HUI2] 0.330 (0.042) 0.300- 0.390 [2]	[TTO] 0.510 (0.016) [1] [HUI3] 0.146 (0.063) 0.010- 0.218 [3]	[CG] 0.590 (0.013) [1]	[EQ-5D] 0.117 (0.101) 0.040- 0.250 [2]
5.13 Eating disorders	[EQ-5D] 0.567 (0.008) 0.560- 0.610 [3]			
5.14 Substance use disorders	[EQ-5D] 0.601 (0.165) 0.470- 0.810 [4]			
ICD-10 Chapter 6: Nervous system disorders				
6.1 Cerebral palsy	[EQ-5D-Y VAS] 86.3 (3.47) [1] [AQoL-5D] 0.276 (0.030) [1]	[TTO] 0.550 (0.016) [1] [HUI2] 0.125 (0.019) [1]	[CG] 0.600 (0.014) [1] [HUI3] 0.363 (0.045) 0.274- 0.420 [3]	[EQ-5D] 0.922 (0.068) [1]
6.2 Muscular dystrophy	[EQ-5D] 0.198 (0.026) [1]	[HUI3] 0.403 (0.118) 0.100- 0.750 [6]		

6.3 Epilepsy	[EQ-5D VAS] 73.6 (0.467) 73.0-74.0 [2] [EQ-5D] 0.633 (0.022) 0.620-0.710 [3]	[TTO] 0.710 (0.013) [1] [EQ-5D-Y] 0.530 (0.069) [1]	[CG] 0.700 (0.012) [1] [HUI2] 0.796 (0.005) 0.790-0.800 [2]	[15D/16D/17D] 0.947 (0.011) [1] [HUI3] 0.552 (0.098) 0.325-0.790 [4]
6.4 Migraine	[EQ-5D VAS] 64.3 (6.05) 62.1-72.7 [2]	[HUI3] 0.900 (0.010) [1]		
6.5 Hydrocephalus	[HUI3] 0.648 (0.046) 0.111-0.910 [7]			
6.6 Combined disorders of the nervous system	[VAS] 23.1 (0.951) 22.0-24.1 [3]	[HUI3] 0.280 (0.065) [1]		
ICD-10 Chapter 7: Disease of the eye				
7.1 Visual disturbances and blindness	[TTO] 0.810 (0.010) [1]	[CG] 0.810 (0.010) [1]	[HUI3] 0.473 (0.077) [1]	
7.2 Other diseases of the eye	[TTO] 0.930 (0.0001) [1]	[CG] 0.850 (0.005) [1]	[HUI3] 0.397 (0.175) 0.050-1.000 [4]	
ICD-10 Chapter 8: Diseases of the ear				
8.1 Moderate hearing loss	[VAS] 54.4 (4.54) 49.2-65.2 [3] [EQ-5D] 0.850 (0.051) 0.630-0.880 [3]	[EQ-5D VAS] 80.2 (1.46) 79.0-82.0 [2] [HUI2] 0.639 (0.028) 0.570-0.650 [2]	[EQ-5D-Y VAS] 88.1 (2.77) [1] [HUI3] 0.601 (0.033) 0.370-0.820 [7]	[QWB] 0.601 (0.011) [1]
8.2 Severe hearing loss	[VAS] 42.1 (4.24) 36.8-59.0 [4]	[TTO] 0.855 (0.024) 0.750-0.860 [2]	[CG] 0.860 (0.009) [1]	[HUI3] 0.496 (0.049) 0.250-0.830 [11]
8.3 Acute otitis media	[VAS] 72.8 (4.92) 53.0-79.0 [4] [EQ-5D] 0.610 (0) 0.610-0.610 [2]	[EQ-5D VAS] 65.4 ((1.29) 65.0-70.0 [2] [HUI2] 0.731 (0.056) 0.650-0.770 [2]	[TTO] 0.970 (0.008) [1] [HUI3] 0.673 (0.078) 0.510-0.710 [2]	[CG] 0.960 (0.007) [1]
8.4 Otitis media with effusion	[EQ-5D] 0.884 (0.039) [1]	[HUI2] 0.879 (0.009) 0.849-0.882 [2]	[HUI3] 0.829 (0.011) [1]	
ICD-10 Chapter 9: Circulatory system disorders				
9.1 Hypertension	[VAS] 48.9 (2.71) 45.1-54.3 [3]	[HUI3] 0.700 (0.115) [1]		
9.2 Stroke	[VAS] 30.0 (1.00) 29.0-31.0 [2]	[SG] 0.772 (0.020) 0.750-0.790 [2]	[HUI3] 0.790 (0.113) [1]	
9.3 Heart disease	[15D/16D/17D] 0.940 [1]	[HUI2] 0.107 (0.136) 0.050-0.760 [3]	[HUI3] 0.766 (0.187) 0.484-0.890 [2]	
ICD-10 Chapter 10: Respiratory system disorders				
10.1 Chronic lower respiratory disease	[VAS] 65.9 (0.555) 64.0-66.3 [3] [SG] 0.910 (0.011) 0.820-0.933 [7] [Modified HUI] 0.890 (0.012) [1]	[EQ-5D VAS] 89.2 (2.67) 79.6-89.9 [2] [CG] 0.830 (0.011) [1] [PAHOM] 0.837 (0.058) 0.700-0.950 [4]	[EQ-5D-Y VAS] 82.6 (2.16) 80.7-85.0 [2] [EQ-5D] 0.901 (0.020) 0.880-0.920 [2]	[TTO] 0.850 (0.011) [1] [HUI3] 0.903 (0.028) 0.553-0.930 [3]
10.2 Influenza and pneumonia	[VAS] 74.8 (4.20) 66.9-83.1 [3] [HUI3] 0.572 (0.019) 0.530-0.580 [2]	[EQ-5D VAS] 67.6 (1.66) 67.0-72.0 [2]	[EQ-5D] 0.477 (0.007) 0.460-0.480 [2]	[HUI2] 0.695 (0.011) 0.690-0.720 [2]

10.3 Laryngotracheal stenosis	[VAS] 90.5 (0.767) 90.0-93.0 [3]	[15D/16D/17D] 0.869 (0.050) [1]	[HUI3] 0.896 (0.038) 0.840-0.970 [3]	
10.4 Upper respiratory infections and diseases	[EQ-5D VAS] 92.3 (0.417) [1]	[CG] 0.897 (0.064) 0.776-0.931 [2]	[15D/16D/17D] 0.933 (0.002) 0.930-0.935 [2]	[HUI3] 0.930 (0.014) [1]
10.5 Combined disorders of respiratory system	[EQ-5D VAS] 67.2 (1.85) 66.0-70.0 [2]	[EQ-5D] 0.572 (0.052) 0.500-0.610 [2]	[HUI2] 0.715 (0.005) 0.710-0.720 [2]	[HUI3] 0.552 (0.035) 0.464-0.580 [3]
ICD-10 Chapter 11: Digestive system disorders				
11.1 Noninfective enteritis and colitis	[VAS] 77.6 (1.98) [1]	[EQ-5D VAS] 91.8 (2.71) 73.6-92.2 [2]	[TTO] 0.923 (0.021) [1]	[SG] 0.971 (0.009) [1]
	[15D/16D/17D] 0.935 (0.017) 0.880-0.950 [3]			
11.2 Congenital diaphragmatic hernia	[EQ-5D] 0.910 (0.104) [1]	[HUI3] 0.906 (0.023) [1]		
11.3 Dental caries	[CHU9D] 0.880 (0.009) [1]			
11.4 Other disorders of the digestive system	[15D/16D/17D] 0.930 [1]	[HUI2] 0.860 [1]	[HUI3] 0.882 (0.075) 0.575-0.900 [2]	
ICD-10 Chapter 12: Diseases of the skin				
12.1 Atopic dermatitis	[VAS] 59.1 (5.12) 58.1-86.3 [2]	[EQ-5D VAS] 92.2 (0.404) [1]	[EQ-5D] 0.690 (0.028) [1]	[PAHOM] 0.690 (0.019) [1]
12.2 Acne	[TTO] 0.961 (0.006) [1]	[HUI3] 0.920 (0.098) [1]		
12.3 Combined skin diseases	[HUI3] 0.621 (0.073) [1]			
ICD-10 Chapter 13: Musculoskeletal system disorders				
13.1 Juvenile idiopathic arthritis	[EQ-5D-Y VAS] 65.6 (4.16) [1]	[EQ-5D] 0.837 (0.104) 0.630-0.889 [2]	[HUI3] 0.730 (0.134) 0.415-0.880 [3]	
13.2 Scoliosis	[EQ-5D] 0.699 (0.129) 0.100-0.760 [3]			
13.3 Hip dysplasia	[EQ-5D VAS] 85.9 (5.63) [1]	[HUI3] 0.830 (0.040) [1]	[SF-6D] 0.894 (0.028) 0.870-0.926 [2]	
13.4 Combined musculoskeletal disorders	[VAS] 76.5 (0.820) 75.0-77.7 [3]	[SG] 0.935 (0.012) [1]	[CG] 0.904 (0.009) 0.890-0.910 [2]	[HUI3] 0.866 (0.039) 0.762-0.880 [2]
ICD-10 Chapter 14: Genitourinary system disorders				
14.1 Kidney failure (after successful kidney transplant)	[VAS] 83.0 (2.71) [1]	[TTO] 0.990 (0.0002) [1]	[15D/16D/17D] 0.885 (0.035) 0.850-0.920 [2]	[HUI2] 0.863 (0.032) [1]
	[HUI3] 0.854 (0.042) [1]			
14.2 Kidney disease (before kidney transplant or after failed transplant)	[VAS] 55.0 (4.23) [1]	[TTO] 0.620 (0.085) [1]	[HUI2] 0.720 (0.056) [1]	[HUI3] 0.714 (0.053) [2]
	[SF-6D] 0.700 (0.027) [1]			
14.3 Inflammatory and non-inflammatory disorders of female pelvic organs	[VAS] 62.0 (3.33) 47.9-73.8 [8]	[EQ-5D VAS] 39.2 (5.68) [1]	[TTO] 0.856 (0.019) 0.760-0.910 [8]	[EQ-5D] 0.750 (0.057) [1]
14.4 Other urogenital disorders	[VAS] 65.4 (0.783) 64.5-67.1 [3]	[HUI3] 0.879 (0.105) 0.611-0.920 [2]		
ICD-10 Chapter 16: Conditions originating in the perinatal period				
16.1 ELBW/EPT without major comorbidity	[VAS] 75.2 (6.58) 50.0-87.0 [5]	[SG] 0.818 (0.025) 0.540-0.960 [22]	[HUI2] 0.895 (0.020) 0.800-0.955 [8]	[HUI3] 0.873 (0.020) 0.750-0.959 [13]

16.2 ELBW/EPT with major comorbidity	[VAS] 26.3 (2.70) 21.0-34.0 [4] [HUI3] 0.726 (0.039) 0.318-0.800 [8]	[SG] 0.206 (0.043) -0.070-0.780 [17]	[CG] 0.900 (0.017) [1]	[HUI2] 0.821 (0.032) 0.612-0.890 [6]
16.3 VLBW/VPT	[15D/16D/17D] 0.943 (0.011) [1]	[HUI3] 0.884 (0.012) 0.840-0.930 [6]		
16.4 Foetal alcohol spectrum disorder	[HUI3] 0.475 (0.030) 0.440-0.500 [2]			
ICD-10 Chapter 17: Congenital malformations				
17.1 Spina bifida	[EQ-5D-Y VAS] 76.9 (6.52) [1]	[AQoL-5D] 0.370 (0.041) [1]	[HUI2] 0.550 (0.027) [1]	[HUI3] 0.521 (0.019) 0.448-0.800 [6]
17.2 Craniosynostosis	[VAS] 84.3 (2.00) 77.0-88.0 [5]	[HUI3] 0.791 (0.055) 0.440-0.870 [5]		
17.3 Other congenital limb, bone and facial deformities	[EQ-5D-Y VAS] 90.1 (3.49) 78.8-93.0 [3] [HUI3] 0.575 (0.222) 0.180-0.700 [2]	[15D/16D/17D] 0.912 (0.004) 0.908-0.916 [2]	[EQ-5D] 0.740 (0.070) [1]	[HUI3] 0.413 (0.022) 0.376-0.471 [4]
17.4 Congenital malformations of the nervous system				
17.5 Imperforate anus	[EQ-5D VAS] 84.1 (0.924) [1]	[EQ-5D] 0.880 (0.001) 0.880-0.890 [2] [HUI3] 0.276 (0.044) 0.162-0.360 [5]		
17.6 Chromosomal abnormalities	[EQ-5D] 0.460 (0.032) [1]			
ICD-10 Chapter 19: Injury, poisoning and other consequences of external causes				
19.1 Survivors of combined types of injuries	[VAS] 14.8 (4.45) 11.0-20.0 [2] [EQ-5D] 0.904 (0.017) 0.610-0.930 [7]	[EQ-5D VAS] 86.8 (2.96) 78.3-90.5 [4] [HUI3] 0.875 (0.007) [1]	[SG] 0.586 (0.020) 0.570-0.610 [2]	[QWB] 0.698 (0.021) 0.672-0.715 [2]
19.2 Survivors of head and facial injuries	[QWB] 0.508 (0.028) [1]	[EQ-5D] 0.959 (0.025) 0.930-0.980 [2]	[HUI2] 0.400 (0.017) [1]	[HUI3] 0.345 (0.098) [1]
19.3 Survivors of other types of injuries	[VAS] 77.0 (3.88) [1]	[15D/16D/17D] 0.962 (0.028) [1]	[EQ-5D] 0.889 (0.014) 0.850-0.920 [5]	
19.4 Allergy	[EQ-5D VAS] 92.6 (0.270) [1] [HUI3] 0.917 (0.007) 0.900-0.920 [2]	[TTO] 0.910 (0.010) [1]	[CG] 0.910 (0.008) [1]	[EQ-5D] 0.840 (0.012) [1]
ICD-10 Chapter 21: Contact with health services				
21.1 Survivors of paediatric intensive care for unspecified reasons	[VAS] 70.0 (11.2) [1] [HUI3] 0.725 (0.067) 0.580-0.810 [3]	[TTO] 0.910 (0.009) [1]	[CG] 0.870 (0.010) [1]	[HUI2] 0.780 (0.029) [1]
21.2 Unspecified organ failure awaiting transplant	[15D/16D/17D] 0.885 (0.006) 0.874-0.888 [2]			
21.3 Palliative care	[HUI2] 0.370 (0.028) [1]	[HUI3] 0.150 (0.042) [1]		
Combined chronic diseases				
22. Combined types of chronic diseases	[VAS] 79.4 (1.03) 76.0-80.0 [3]	[EQ-5D VAS] 72.9 (0.267) 71.7-73.0 [2]	[EQ-5D-Y VAS] 84.4 (2.54) 74.6-88.4 [4]	[TTO] 0.890 (0.024) 0.770-0.920 [3]

[SG] 0.924 (0.003) 0.920- 0.930 [3] [HUI2] 0.884 (0.034) 0.760- 0.950 [4]	[CG] 0.960 (0.016) [1] [HUI3] 0.834 (0.098) 0.142- 0.920 [4]	[15D/16D/17D] 0.895 (0.013) [1]	[EQ-5D] 0.800 (0.012) [1]
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[Valuation method] Mean (Standard error) Range [Number of samples]. VAS scores expressed to three significant figures; utility values expressed to three decimal places. Where two or more samples are used to calculate the weighted average, standard error measures the degree of variation between samples. Where only one sample is used, the standard error of the sample mean is taken. CG: Chained Gamble. ELBW/EPT: Extremely-low birthweight or extremely preterm birth. VLBW/VPT: Very-low birthweight or very preterm birth.

Table 4: Meta-regression of main health utility samples measured using the HUI3; hierarchical linear model

Variable	Coefficient	Robust standard error	95% confidence interval	P value
Constant (Baseline scenario)	0.876	0.045	0.788 to 0.965	<0.001
ICD-10 Chapter 1: Infectious and parasitic diseases				
1.2 Viral infections of central nervous system	-0.568	0.059	-0.684 to -0.452	<0.001
1.4 Meningococcal infection with permanent sequelae	-0.424	0.071	-0.564 to -0.285	<0.001
1.7 Bacteremia	-0.295	0.071	-0.434 to -0.156	<0.001
ICD-10 Chapter 2: Cancer				
2.1 Survivors of combined types of cancer	0.019	0.028	-0.036 to 0.073	0.498
2.2 Patients of combined types of cancer on active therapy	-0.298	0.041	-0.378 to -0.218	<0.001
2.3 Survivors of acute lymphoblastic leukaemia	0.024	0.006	0.013 to 0.036	<0.001
2.4 Patients of acute lymphoblastic leukaemia on active therapy	-0.202	0.006	-0.213 to -0.190	<0.001
2.5 Survivors of brain tumour	-0.074	0.004	-0.081 to -0.066	<0.001
2.6 Patients of brain tumour on active therapy	-0.480	0.028	-0.534 to -0.425	<0.001
2.7 Survivors of lymphoma	0.025	0.005	0.016 to 0.035	<0.001
2.8 Patients of lymphoma on active therapy	-0.334	0.005	-0.344 to -0.325	<0.001
2.9 Survivors of renal tumour	0.067	0.003	0.061 to 0.073	<0.001
2.10 Survivors of retinoblastoma	0.037	0.003	0.032 to 0.043	<0.001
2.11 Survivors of sympathetic nervous system tumour	0.057	0.003	0.051 to 0.063	<0.001
2.12 Survivors of other types of cancer	0.015	0.003	0.009 to 0.020	<0.001
ICD-10 Chapter 3: Diseases of the blood and immune system				
3.3 Combined diseases of the blood	-0.237	0.059	-0.353 to -0.121	<0.001
ICD-10 Chapter 4: Endocrine, nutritional and metabolic disorders				
4.1 Overweight	-0.015	0.005	-0.025 to -0.006	0.002
4.2 Obese or Diabetes type II	-0.032	0.019	-0.069 to 0.005	0.087
4.3 Diabetes type I	-0.230	0.037	-0.301 to -0.158	<0.001
4.4 Cystic fibrosis	-0.014	0.059	-0.130 to 0.102	0.807
4.8 Other metabolic disorders ^a	-0.413	0.036	-0.484 to -0.342	<0.001
ICD-10 Chapter 5: Mental and behavioural disorders				
5.1 Attention-deficit hyperactivity disorder	-0.369	0.039	-0.445 to -0.292	<0.001
5.2 Autism spectrum disorder	-0.367	0.036	-0.438 to -0.297	<0.001
5.3 Other pervasive developmental disorders ^b	-0.258	0.035	-0.327 to -0.189	<0.001
5.5 Behavioural disorders	-0.318	0.048	-0.412 to -0.225	<0.001
5.6 Stress-related and somatoform disorders	-0.272	0.015	-0.301 to -0.243	<0.001
5.8 Other mental disorders ^c	-0.247	0.014	-0.274 to -0.219	<0.001
5.9 Disorders of speech and language	-0.364	0.036	-0.435 to -0.292	<0.001
5.10 Disorders of scholastic skills	-0.376	0.047	-0.468 to -0.284	<0.001
5.11 Cognitive impairment	-0.400	0.014	-0.427 to -0.372	<0.001
5.12 Mental retardation	-0.600	0.033	-0.664 to -0.536	<0.001
ICD-10 Chapter 6: Nervous system disorders				
6.1 Cerebral palsy	-0.528	0.036	-0.599 to -0.457	<0.001
6.2 Muscular dystrophy	-0.358	0.059	-0.474 to -0.242	<0.001
6.3 Epilepsy	-0.324	0.123	-0.565 to -0.083	0.008
6.4 Migraine	-0.068	0.026	-0.119 to -0.017	0.009

6.5 Hydrocephalus	-0.629	0.060	-0.748 to -0.511	<0.001
6.6 Other disorders of the nervous system ^d	-0.462	0.059	-0.578 to -0.346	<0.001
ICD-10 Chapter 7: Diseases of the eye				
7.1 Vision loss	-0.329	0.036	-0.400 to -0.258	<0.001
7.2 Other diseases of the eye ^e	0.031	0.027	-0.022 to 0.084	0.249
ICD-10 Chapter 8: Diseases of the ear				
8.1 Moderate hearing loss	-0.284	0.057	-0.395 to -0.173	<0.001
8.2 Severe hearing loss	-0.360	0.056	-0.470 to -0.250	<0.001
8.3 Acute otitis media	-0.178	0.071	-0.317 to -0.039	0.012
8.4 Otitis media with effusion	0.008	0.047	-0.084 to 0.099	0.864
ICD-10 Chapter 9: Circulatory system disorders				
9.1 Hypertension	-0.168	0.026	-0.219 to -0.117	<0.001
9.2 Stroke	-0.178	0.026	-0.229 to -0.127	<0.001
9.3 Heart disease	-0.158	0.104	-0.362 to 0.045	0.128
ICD-10 Chapter 10: Respiratory system disorders				
10.1 Chronic lower respiratory diseases	-0.074	0.049	-0.169 to 0.021	0.127
10.2 Influenza and pneumonia	-0.259	0.071	-0.397 to -0.120	<0.001
10.3 Laryngotracheal stenosis	0.044	0.022	0.000 to 0.087	0.043
10.4 Upper respiratory infections and diseases	-0.038	0.026	-0.089 to 0.013	0.147
10.5 Combined disorders of the respiratory system	-0.273	0.065	-0.399 to -0.146	<0.001
ICD-10 Chapter 11: Digestive system disorders				
11.2 Congenital diaphragmatic hernia	0.047	0.024	0.001 to 0.094	0.042
11.4 Other disorders of the digestive system ^f	-0.091	0.058	-0.205 to 0.024	0.121
ICD-10 Chapter 12: Diseases of the skin				
12.2 Acne	-0.048	0.026	-0.099 to 0.003	0.067
12.3 Combined skin diseases	-0.181	0.036	-0.252 to -0.110	<0.001
ICD-10 Chapter 13: Musculoskeletal system disorders				
13.1 Juvenile idiopathic arthritis	-0.155	0.104	-0.359 to 0.049	0.136
13.3 Hip dysplasia	0.028	0.025	-0.022 to 0.077	0.272
13.4 Combined musculoskeletal disorders ^g	-0.088	0.026	-0.139 to -0.037	0.001
ICD-10 Chapter 14: Genitourinary system disorders				
14.1 Kidney failure (after successful kidney transplant)	0.111	0.046	0.020 to 0.201	0.016
14.2 Kidney disease (before kidney transplant or after failed transplant)	-0.138	0.059	-0.254 to -0.022	0.019
14.4 Other urogenital disorders ^h	-0.094	0.074	-0.238 to 0.050	0.202
ICD-10 Chapter 16: Conditions originating in the perinatal period				
16.1 ELBW/EPT without major comorbidity	-0.081	0.037	-0.154 to -0.009	0.029
16.2 ELBW/EPT with major comorbidity	-0.268	0.065	-0.396 to -0.141	<0.001
16.3 VLBW/VPT	-0.021	0.014	-0.047 to 0.006	0.126
16.4 Foetal alcohol spectrum disorder	-0.330	0.025	-0.379 to -0.281	<0.001
ICD-10 Chapter 17: Congenital malformations				
17.1 Spina bifida	-0.294	0.059	-0.410 to -0.178	<0.001
17.2 Craniosynostosis	-0.146	0.046	-0.236 to -0.057	0.001
17.3 Other congenital limb, bone and facial deformities ⁱ	-0.344	0.053	-0.448 to -0.240	<0.001
17.4 Congenital malformations of the nervous system	-0.622	0.036	-0.693 to -0.551	<0.001
17.6 Chromosomal abnormalities	-0.504	0.045	-0.593 to -0.416	<0.001
ICD-10 Chapter 19: Injury, poisoning and other consequences of external causes				
19.1 Survivors of combined types of injuries	-0.067	<0.001	-0.067 to -0.067	<0.001

19.2 Survivors of head and facial injuries	-0.397	0.059	-0.513 to -0.281	<0.001
19.4 Allergy	-0.054	0.026	-0.105 to -0.003	0.039
ICD-10 Chapter 21: Contact with health services				
21.1 Survivors of paediatric intensive care for unspecified reasons	-0.258	0.041	-0.338 to -0.178	<0.001
21.3 Palliative care	-0.859	0.028	-0.913 to -0.804	<0.001
Combined chronic diseases				
22. Combined types of chronic diseases	-0.642	0.054	-0.748 to -0.536	<0.001
Dummy for hypothetical health state	-0.098	0.078	-0.251 to 0.054	0.205
Respondent types. Baseline: Self-assessment by children/adolescents				
Assessed together by children/adolescents and parents or by children/adolescents and caregivers	-0.055	0.016	-0.086 to -0.025	<0.001
Proxy-assessment by parents	0.041	0.012	0.017 to 0.065	0.001
Proxy-assessment by caregivers	-0.053	0.015	-0.082 to -0.024	<0.001
Proxy-assessment by physicians or by physicians and caregivers	0.090	0.047	-0.001 to 0.182	0.054
Proxy-assessment by nurses	0.121	0.139	-0.153 to 0.394	0.387
Administration modes. Baseline: Self-administered in health or school setting				
Self-administered postal survey	0.043	0.044	-0.042 to 0.129	0.323
Self-administered online survey	-0.015	0.053	-0.119 to 0.088	0.772
Face-to-face interview	-0.019	0.044	-0.104 to 0.067	0.669
Telephone interview	0.151	0.047	0.059 to 0.244	0.001
Administration mode not specified	0.061	0.045	-0.026 to 0.148	0.170
Dummy for samples with minimum age greater than 12	-0.060	0.028	-0.115 to -0.005	0.033
Dummy for samples from developing countries	-0.057	0.046	-0.147 to 0.034	0.219
<p>Note. 278 samples across 88 studies included. Dependent variable: mean HUI3. Individual mean HUI3 utilities weighted by inverse of standard error and each study weighted by total number of respondents. Baseline scenario (interpretation of constant): samples with general population health, self-assessed by children/adolescents, self-administered survey (non-postal questionnaire or Delphi process), non-hypothetical health state, minimum age less than 12 and from developed countries (Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, New Zealand, Portugal, Singapore, Sweden, UK and US). ELBW/EPT: Extremely-low birthweight or extremely preterm birth. VLBW/VPT: Very-low birthweight or very preterm birth. Main samples using HUI3 included in the following categories: ^aCategory 4.8 – Mucopolysaccharidosis type II (Hunter Syndrome) and Combined metabolic disorders; ^bCategory 5.3 – Asperger’s syndrome and Combined pervasive developmental disorders; ^cCategory 5.8 – Combined psychiatric disorders (diagnosed by DSM-IV); ^dCategory 6.6 – Combined rare disorders of the central nervous system; ^eCategory 7.2 – Combined disorders of eye, Nystagmus, Visual pathway impairment and Cataracts; ^fCategory 11.4 – Gastric ulcer and Combined digestive disorders; ^gCategory 13.4 – Back pain and Combined musculoskeletal disorders; ^hCategory 14.4 – Combined urogenital disorders and Urinary incontinence; ⁱCategory 17.3 – Combined bone deformities, Osteogenesis imperfecta and other bone deformities, Congenital skeletal and facial conditions and Congenital conditions of the connective tissue.</p>				

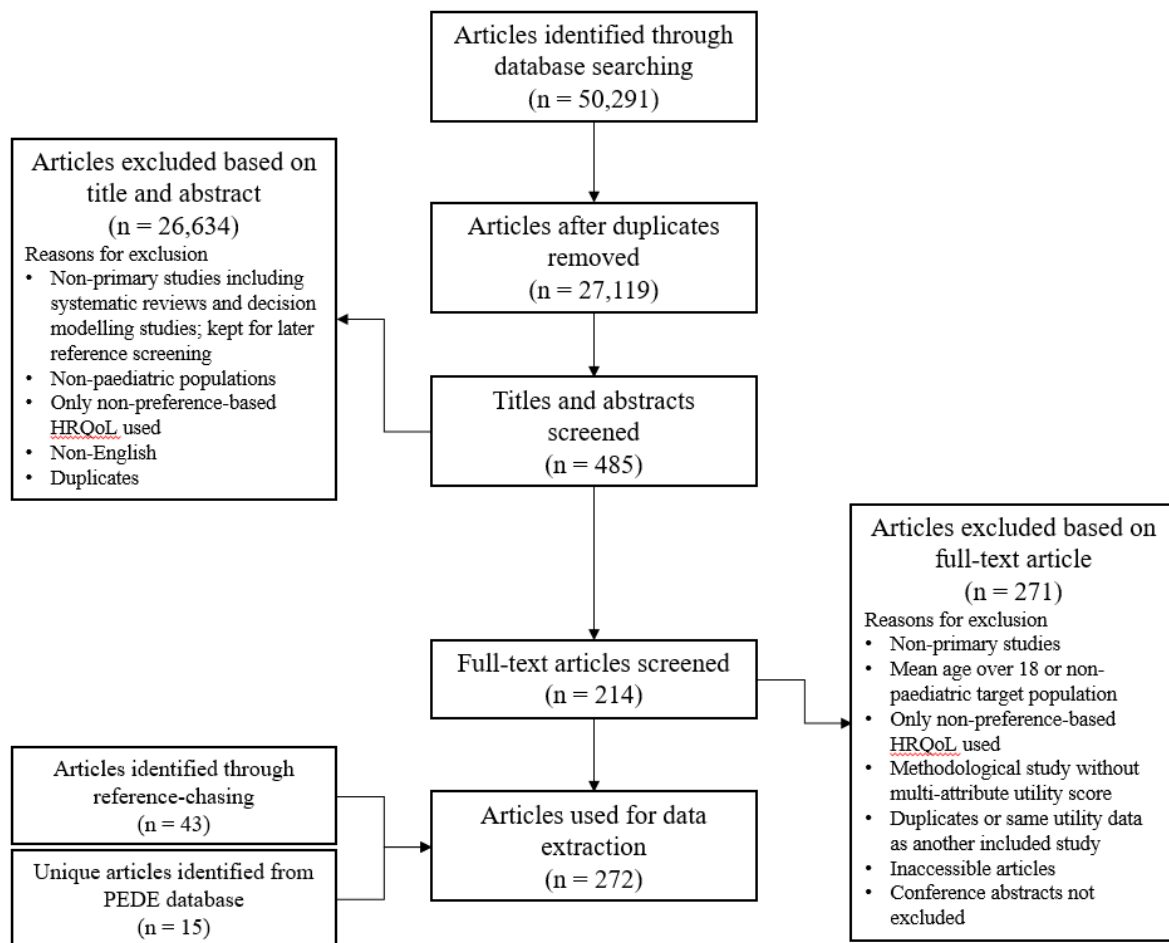
Table 5: Meta-regression of main health utility samples measured using a VAS; hierarchical linear model

Variable	Coefficient	Robust standard error	95% confidence interval	P value
Constant (Baseline scenario)	82.88	1.28	80.36 to 85.39	<0.001
ICD-10 Chapter 1: Infectious and parasitic diseases				
1.1 Gastroenteritis	-39.80	2.53	-44.75 to -34.84	<0.001
1.2 Viral infections of central nervous system	-21.58	5.90	-33.14 to -10.03	<0.001
1.4 Meningococcal infection with permanent sequelae	-22.66	6.29	-34.99 to -10.33	<0.001
1.6 Viral fever	-8.43	5.90	-19.99 to 3.13	0.153
1.7 Bacteremia	-20.01	5.64	-31.05 to -8.96	<0.001
ICD-10 Chapter 2: Cancer				
2.2 Patients of combined types of cancer on active therapy	-3.80	1.63	-7.00 to -0.60	0.020
2.4 Patients of acute lymphoblastic leukaemia on active therapy	-9.31	3.07	-15.32 to -3.30	0.002
2.7 Survivors of lymphoma	12.58	2.45	7.77 to 17.38	<0.001
2.8 Patients of lymphoma on active therapy	-16.42	2.45	-21.23 to -11.62	<0.001
ICD-10 Chapter 3: Diseases of the blood and immune system				
3.1 Haemophilia	-25.17	13.86	-52.34 to 2.00	0.069
3.2 Haemolytic anaemias	-9.00	<0.001	-9.00 to -9.00	<0.001
ICD-10 Chapter 4: Endocrine, nutritional and metabolic disorders				
4.1 Overweight	-3.28	0.59	-4.44 to -2.12	<0.001
4.2 Obese or Diabetes type II	-6.32	1.33	-8.92 to -3.72	<0.001
4.3 Diabetes type I	-12.63	3.16	-18.81 to -6.44	<0.001
4.4 Cystic fibrosis	-0.38	2.39	-5.06 to 4.30	0.873
ICD-10 Chapter 5: Mental and behavioural disorders				
5.1 Attention-deficit hyperactivity disorder	-26.88	4.72	-36.13 to -17.62	<0.001
5.2 Autism spectrum disorder	-10.88	5.48	-21.62 to -0.15	0.047
5.4 Depression	-26.44	2.54	-31.42 to -21.46	<0.001
5.5 Behavioural disorders	-20.14	6.06	-32.02 to -8.25	0.001
5.6 Stress-related and somatoform disorders	-2.41	4.79	-11.79 to 6.97	0.615
5.9 Disorders of speech and language	-1.97	2.48	-6.83 to 2.89	0.427
5.10 Disorders of scholastic skills	-14.73	6.06	-26.61 to -2.85	0.015
5.12 Mental retardation	-21.35	5.75	-32.61 to -10.08	<0.001
ICD-10 Chapter 6: Nervous system disorders				
6.1 Cerebral palsy	-7.23	3.19	-13.48 to -0.97	0.024
6.3 Epilepsy	-6.72	5.61	-17.72 to 4.29	0.232
6.4 Migraine	-23.16	2.25	-27.56 to -18.75	<0.001
6.6 Combined disorders of the nervous system	-47.05	5.90	-58.61 to -35.50	<0.001
ICD-10 Chapter 8: Diseases of the ear				
8.1 Moderate hearing loss	-11.71	7.21	-25.85 to 2.43	0.104
8.2 Severe hearing loss	-30.63	5.70	-41.80 to -19.47	<0.001
8.3 Acute otitis media	-12.77	5.63	-23.81 to -1.72	0.023
ICD-10 Chapter 9: Circulatory system disorders				
9.1 Hypertension	-20.75	5.90	-32.31 to -9.20	<0.001
9.2 Stroke	-20.82	4.97	-30.56 to -11.09	<0.001
ICD-10 Chapter 10: Respiratory system disorders				
10.1 Chronic lower respiratory disease	-5.71	0.20	-6.10 to -5.31	<0.001

10.2 Influenza and pneumonia	3.05	6.07	-8.84 to 14.94	0.615
10.3 Laryngotracheal stenosis	-0.56	2.76	-5.97 to 4.86	0.841
10.4 Upper respiratory infections and diseases	-3.42	0.09	-3.59 to -3.25	<0.001
10.5 Combined disorders of the respiratory system	-12.11	5.64	-23.16 to -1.05	0.032
ICD-10 Chapter 11: Digestive system disorders				
11.1 Noninfective enteritis and colitis	-3.57	0.08	-3.73 to -3.42	<0.001
ICD-10 Chapter 12: Diseases of the skin				
12.1 Atopic dermatitis	-3.51	0.11	-3.72 to -3.30	<0.001
ICD-10 Chapter 13: Musculoskeletal system disorders				
13.1 Juvenile idiopathic arthritis	-28.23	3.19	-34.48 to -21.97	<0.001
13.3 Hip dysplasia	2.48	2.54	-2.50 to 7.47	0.328
13.4 Combined musculoskeletal disorders ^a	-17.39	2.30	-21.89 to -12.89	<0.001
ICD-10 Chapter 14: Genitourinary system disorders				
14.1 Kidney failure (after successful kidney transplant)	-1.60	4.24	-9.92 to 6.72	0.706
14.2 Kidney disease (before kidney transplant or after failed transplant)	-29.60	4.24	-37.92 to -21.28	<0.001
14.3 Inflammatory and non-inflammatory disorders of female pelvic organs	7.52	3.25	1.14 to 13.89	0.021
14.4 Other urogenital disorders ^b	-4.70	5.90	-16.25 to 6.86	0.426
ICD-10 Chapter 16: Certain conditions originating in the perinatal period				
16.1 ELBW/EPT without major comorbidity	-0.65	3.57	-7.65 to 6.35	0.856
16.2 ELBW/EPT with major comorbidity	-43.05	3.61	-50.14 to -35.97	<0.001
ICD-10 Chapter 17: Congenital malformations				
17.1 Spina bifida	-16.93	3.19	-23.18 to -10.67	<0.001
17.2 Craniosynostosis	-6.91	2.48	-11.76 to -2.05	0.005
17.3 Other congenital limb, bone and facial deformities ^c	-5.91	3.19	-12.17 to 0.34	0.064
17.5 Imperforate anus	3.85	4.71	-5.38 to 13.07	0.414
ICD-10 Chapter 19: Injury, poisoning and other consequences of external causes				
19.1 Survivors of combined types of injuries	-10.08	11.58	-32.77 to 12.62	0.384
19.3 Survivors of other types of injuries	1.46	4.16	-6.68 to 9.61	0.725
19.4 Allergy	-3.12	0.09	-3.29 to -2.95	<0.001
ICD-10 Chapter 21: Contact with health services				
21.1 Survivors of paediatric intensive care for unspecified reasons	-20.34	2.48	-25.20 to -15.48	<0.001
Combined chronic diseases				
22. Combined types of chronic diseases	-2.95	0.31	-3.56 to -2.34	<0.001
Dummy for hypothetical health states	-20.51	3.60	-27.56 to -13.46	<0.001
Respondent types. Baseline: Self-assessment by children/adolescents				
Assessed together by children/adolescents and parents or by children/adolescents and caregivers	1.19	4.87	-8.35 to 10.72	0.807
Proxy-assessment by parents	7.43	2.67	2.21 to 12.66	0.005
Proxy-assessment by caregivers	-3.04	4.97	-12.78 to 6.69	0.540
Proxy-assessment by physicians or by physicians and caregivers	13.17	2.63	8.01 to 18.33	<0.001
Proxy-assessment by nurses	-1.48	2.43	-6.24 to 3.28	0.543
Proxy-assessment by general public, by parents from general public or by adult patients	7.02	2.64	1.85 to 12.19	0.008
Administration modes. Baseline: Self-administered in health or school setting				
Self-administered postal survey	4.63	2.44	-0.15 to 9.41	0.058
Self-administered online survey	-7.91	4.18	-16.10 to 0.27	0.058

Face-to-face interview	5.99	2.34	1.40 to 10.58	0.011
Administration mode not specified	18.58	2.45	13.77 to 23.38	<0.001
Dummy for samples with minimum age greater than 12	-5.45	2.44	-10.24 to -0.67	0.026
Dummy for samples from developing countries	-0.49	2.52	-5.43 to 4.45	0.847
Note. 212 samples across 66 studies included. Dependent variable: mean VAS. Individual mean VAS score weighted by inverse of standard error and each study weighted by total number of respondents. Baseline scenario (interpretation of constant): samples with general population health, self-assessed by children/adolescents, self-administered survey (non-postal questionnaire or Delphi process), non-hypothetical health state, minimum age less than 12 and from developed countries (Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Netherlands, New Zealand, Portugal, Singapore, Sweden, UK and US). ELBW/EPT: Extremely-low birthweight or extremely preterm birth. Main samples using VAS included in the following categories: ^a Category 13.4 – Combined musculoskeletal disorders; ^b Category 14.4 – Urinary tract infection; ^c Category 17.3 – Achondroplasia, Arthrogryposis multiple congenital and Combined lower limb deformities				

Figure 1: PRISMA flow diagram



Note. PRISMA: Preferred reporting items for systematic reviews and meta-analyses. HRQoL: Health-related quality of life. PEDE: Pediatric Economic Database Evaluation